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Organocatalytic Conjugate Addition of Nitroalkanes to 3-Ylidene Oxindoles: A Stereocontrolled Diversity Oriented Route to Oxindole Derivatives

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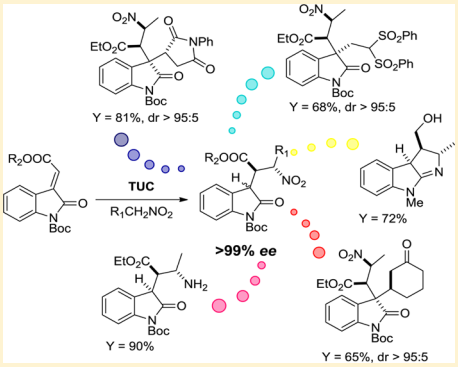
Supporting Information

ABSTRACT: An efficient and highly enantioselective Michael addition of nitroalkanes to 3-ylidene oxindoles is described, mediated by thiourea-based bifunctional organocatalysts. The stereochemistry at C_α and C_β centers is perfectly controlled, and the intermediate C-3 enolate is trapped with a second Michael acceptor. The developed one-pot three-component consecutive reactions generate up to four contiguous stereocenters, including the C-3 all-carbon quaternary center, in a perfectly defined configuration. The conversion of the β-nitro oxindole into the corresponding β-amino derivative discloses synthetically useful transformations, exploitable to generate pharmaceutically attractive molecular targets.



INTRODUCTION

The oxindole scaffold characterizes a large number of natural and synthetic compounds with important biological activities[1,2] (Figure 1).

Therefore, considerable efforts have been devoted to design strategies to synthesize these challenging structures.[3] The potential medicinal significance of these enantiopure backbones has prompted the development of asymmetric approaches, by means of chiral metal catalysts[4] and, more recently, organocatalysts.[5] A main challenge in these approaches is the construction of the chiral backbone often containing sequences of stereocenters, including quaternary centers.[6] In particular, a chiral quaternary center at the 3-position of the oxindole ring is a structural feature of almost all these bioactive scaffolds. In the past few years a huge number of contributions has been published in this field. Currently, there are two[7] main organocatalytic strategies to address the C-3 all-carbon quaternary stereocenter, which exploit the electrophilic or nucleophilic character of the selected oxindole substrate, respectively (Scheme 1).

The first strategy is based on the preliminary nucleophilic conjugate addition to exocyclic α,β-unsaturated oxindole followed by spirocyclization,[8,9] as shown in Scheme 1, eq 1. Alternatively, the nucleophilicity of C-3 is exploited, typically starting from racemic C-3 monosubstituted derivatives[10] (Scheme 1, eq 2a). Domino spiroannulations are again possible when an electrophilic function is present on the C-3 side chain[11] (Scheme 1, eq 2b). Spirocyclizations (Scheme 1, eqs 1 and 2b) are the most frequently exploited approaches, where the chirality generated in the first step controls the formation of the adjacent stereocenters. On the other hand, the reported intermolecular additions[10,12] (Scheme 1, eq 2a) bypass the generation of a stereolabile tertiary center at C-3, directly assembling the chiral quaternary center at this position. Since the conjugate addition shown in Scheme 1, eq 3 provides a poor control of the C-3 stereochemistry, there are very few studies of organocatalytic asymmetric intermolecular additions to the β-carbon of 3-ylidene oxindoles. Xiao and co-workers[13] reported the conjugate addition of acetylacetone to 3-ylidene oxindoles, and using nitromethane as a Michael donor, the expected product was obtained in high yield and enantiocontrol at C_α, but in almost identical amounts of the two diastereoisomers due to lack of control at C-3.

As part of our ongoing investigation into the stereoselective addition of nitroalkanes to α,β-unsaturated systems[14] promoted by bifunctional thiourea-based organocatalysts,[15] we set out to develop the Michael addition of nitroalkanes (**1**) to 3-ylidene oxindoles (**2**) to access highly stereoenriched C-3 β-nitro oxindoles (**3**) (Scheme 2, eq 1). Following a "diversity-oriented synthesis" (DOS)[16] approach, we checked the opportunities offered by the adducts so generated to create structural diversification in chiral 3,3′-disubstituted oxindoles.

It is noteworthy that the C-3 β-nitro oxindole core was usually synthesized by exploiting conjugate additions to nitroalkenes[4,5,8−11] (Scheme 2, eq 2). Very few authors[8j,12a,13] explored the complementary reactivity between nitroalkanes and 3-ylidene oxindoles, which was exploited in our approach (Scheme 2, eq 1).

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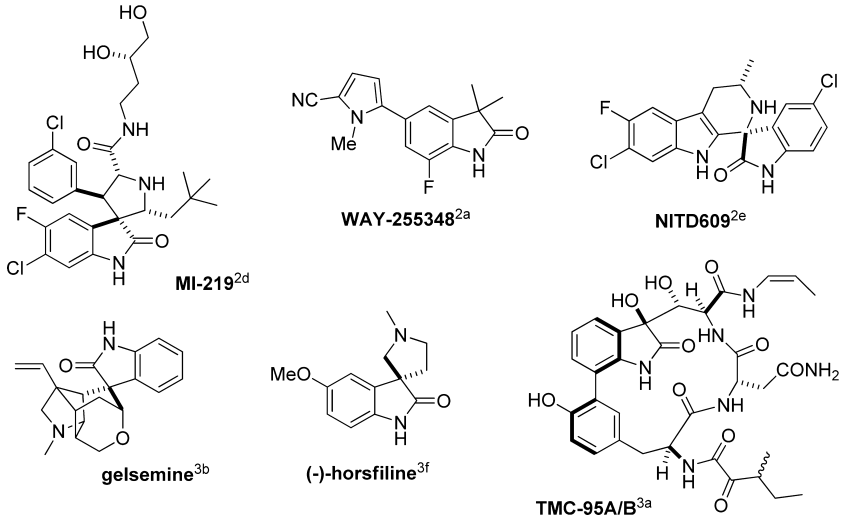
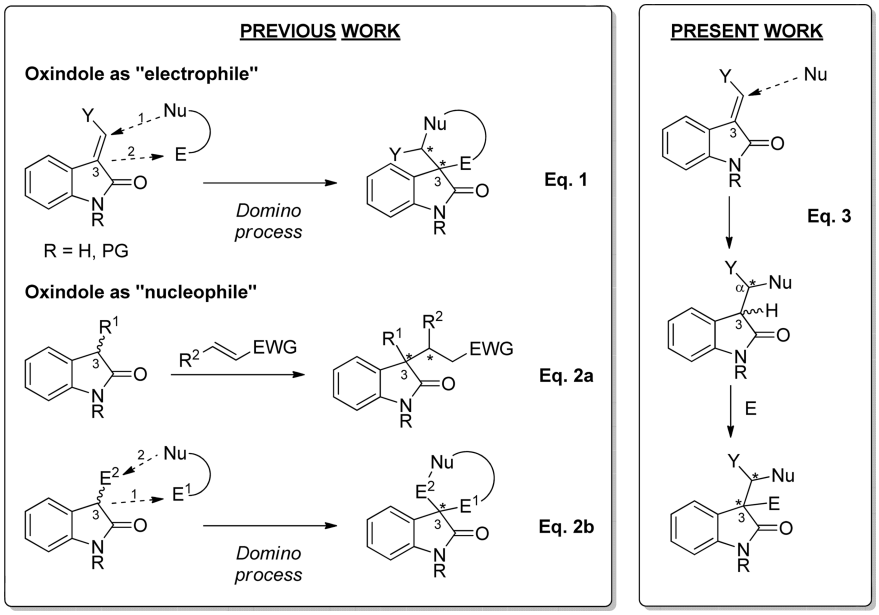


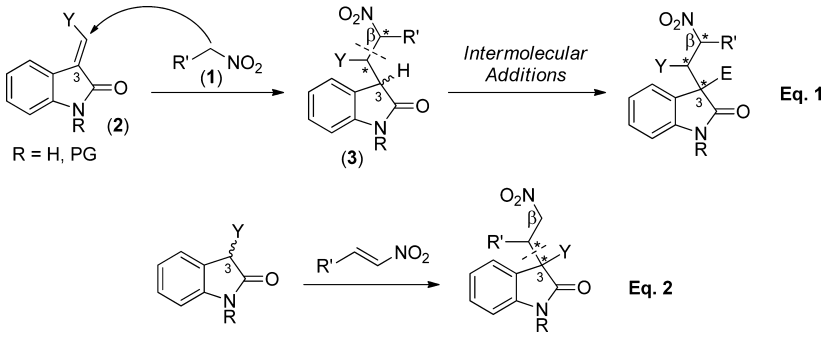
Figure 1. Representative natural and synthetic bioactive products containing the oxindole skeleton.

Scheme 1. Organocatalytic Strategies Employed To Asymmetrically Generate an All-Carbon Quaternary Stereocenter on the C-3 Oxindole Position[a]



[a]Abbreviations: Nu = nucleophilic site; E, E^1, E^2 = electrophilic sites; EWG = electron-withdrawing group; Y = generic substituent.

Scheme 2. Our Asymmetric Approach (Eq 1) to C-3 β-Nitro Oxindole Scaffolds in Comparison with the Most Investigated Approach in the Literature (Eq 2)



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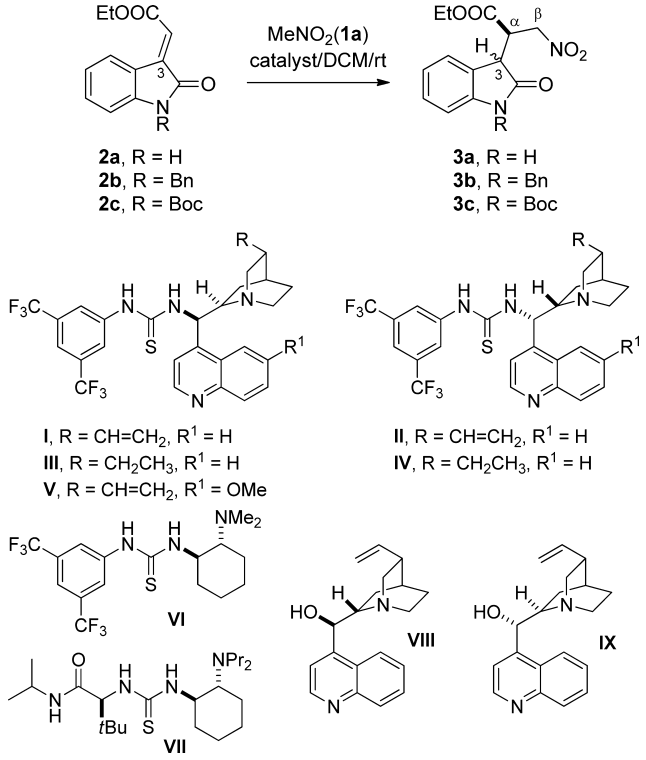
RESULTS AND DISCUSSION

Initially we focused our attention on the addition of nitromethane (**1a**) to differently *N*-substituted (*E*)-ethyl 2-(2-oxoindolin-3-ylidene)acetates (**2a−c**) by using the bifunctional *Cinchona*-derived organocatalyst **I**. As summarized in Table 1,

Table 1. *N*-Protecting Groups and Catalysts Screening in the Organocatalyzed Asymmetric Conjugate Addition of 1a to 3-Ylidene Oxindoles (2a−c)[a]



entry	substrate	catalyst	time (h)	conversn (%)[b]	dr[b]	ee (%)[c]
1	**2a**	**I**	1.5	92	51/49	93/92
2	**2b**	**I**	1.75	99	49/51	92/93
3	**2c**	**I**	1	99	55/45	99/>99
4	**2c**	**II**	1.5	91	48/52	97/98[d]
5	**2c**	**III**	1.75	99	48/52	95/96
6	**2c**	**IV**	1.5	99	55/45	97/97[d]
7	**2c**	**V**	1.5	99	57/43	98/98
8	**2c**	**VI**	1	99	52/48	99/>99
9	**2c**	**VII**	1.5	99	54/46	59/64
10	**2c**	**VIII**	1.5	99	55/45	82/86
11	**2c**	**IX**	2	99	53/47	83/86[d]

[a]Reaction conditions: **2** (0.1 mmol), **1a** (1 mmol), catalyst (10 mol %), dichloromethane (DCM, 0.15 mL), room temperature. [b]Determined by ^{1}H NMR of the crude mixture. [c]Determined by chiral stationary phase (CSP) HPLC of **3**, isolated as a mixture of two C-3 epimers; ee values refer to the two C-3 epimers. [d]Opposite enantiomers were formed.

the employed conditions allowed us to perform reactions much more quickly than those reported by Xiao[13] (90% yield after 15 h), and complete conversions were recorded within only 2 h with all of the substrates **2a−c** (entries 1−3).

As expected, the diastereomeric ratio (dr) was very poor, even if associated with a high enantiomeric excess (ee) for both of the diastereoisomers. Since the best enantioselectivity was achieved for the *N*-Boc substrate **2c** (entry 3), further optimization was performed on it. However, we were pleased to note that just slightly lower ees were obtained for unprotected starting material **2a** (entry 1). This is a noteworthy result, since most of the reported reactions work well on *N*-protected substrates only. Other bifunctional organocatalysts (**II−IX**, Table 1) were tested in the model reaction on substrate **2c**, and high conversions in short reaction times were invariably observed (entries 4−11). Diastereo- and enantioselectivity did not undergo significant changes when *Cinchona*-derived thioureas (**II−V**) and Takemoto's thiourea (**VI**) were used (entries 4−8). Significant lower ees were recorded employing *Cinchona* alkaloids **VIII** and **IX** (entries 10 and 11), and even worse results were obtained with particularly Jacobsen's thiourea **VII** (entry 9). The best results in terms of reaction rate and stereocontrol were obtained with catalysts **I** and **VI**; thus, further optimization was carried out using the low-cost, commercially available Takemoto thiourea **VI**.

The reaction conditions were deeply investigated to understand the effects of nitromethane equivalents, catalyst loading, solvent, and temperature on both the rate and the stereoselection of the process. Selected data are summarized in Table 2.

When the amount of nitromethane (entry 1) and the catalyst loading (entry 2) were individually lowered, and also when they were simultaneously decreased up to 2.5 equiv of **1a** and 2.5 mol % of **VI** (entries 3 and 4), we still got excellent results. The reaction time increased but still was reasonable when 2 equiv of **1a** and only 1 mol % of catalyst (entry 5) were used. Some solvents were also screened, without significant changes in the reaction performance. Finally we lowered the temperature (entries 6 and 7), but we did not observe any improvement in the diastereoselection. From these results we can infer that our reaction system did not allow a stereoselective C-3 protonation. Indeed the C3−H acidity of 3-alkyl-substituted oxindoles might be significantly influenced by the *N*-protecting group.[17] Electron-withdrawing protecting groups increase the acidity of the C-3 position; for instance, the pK_a value of *N*-acetyloxindole is around 13. Hence, the *N*-Boc protection could favor a C-3 epimerization under our reaction conditions.[18]

To expand the reaction scope, we applied our protocol to a variety of 3-ylidene oxindoles (**2c−n**), and we were delighted to find that the process tolerated different substitution patterns very well (Table 3). The employed conditions, representing the best balance of reaction rate and stereocontrol for the different substrates, were identified with 5 equiv of **1a** and 5 mol % of catalyst **VI**. The reactions smoothly proceeded when the aromatic ring was decorated with both electron-withdrawing (entries 2−5) and electron-donating (entry 6) groups. In addition, the substituent position on the ring did not affect the efficiency of the process (cf. entries 2 and 4 and entries 3 and 5). The ethyl ester could be replaced by benzyl (entry 7) and *tert*-butyl (entry 8) esters. So far, good yields and excellent enantioselectivities (up to >99% ee) were reached for both diastereoisomers of the *β*-nitro indolin-2-ones (**3c−j**).

Significant changes, mainly in the enantiocontrol, were observed when, instead of the ester function, aromatic or aliphatic groups were located at the exocyclic double bond. For the phenyl derivative **3k** the ee dropped to 60% (Table 3, entry 9) and the addition of an electron-withdrawing substituent on the phenyl ring provided even worse results (entry 10). The last attempt was conducted on introducing an aliphatic group on the double bond; however, we obtained very poor ees and longer reaction times (entry 11). The latter data suggested that a crucial role for the enantioselectivity was played by the presence of an ester on the 3-ylidene oxindole. According to the dual activation model[19] proposed by Takemoto[19a] and Deng[19b] and theoretical

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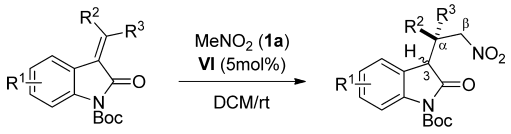
Table 2. Optimization of the Reaction Conditions for the Organocatalyzed Asymmetric Conjugate Addition of 1a to 3-Ylidene Oxindole 2c[a]

entry	amt of **1a** (equiv)	amt of **VI** (mol %)	T (°C)	time (h)	conversn (%)[b]	dr[b]	ee (%)[c]
1	2.5	10	room temp	1	99	57/43	97/>99
2	10	1	room temp	1.5	99	52/48	>99/99
3	5	5	room temp	1	99	53/47	99/99
4	2.5	2.5	room temp	2	99	52/48	98/98
5	2	1	room temp	5.5	72	52/48	95/95
6	5	5	0	1.5	99	49/51	>99/>99
7	5	5	−20	120	72	47/53	>99/>99

[a]Reaction conditions: **2c** (0.1 mmol), catalyst **VI**, DCM (0.15 mL). [b]Determined by ^{1}H NMR of the crude mixture. [c]Determined by CSP-HPLC of **3c**, isolated as a mixture of two C-3 epimers; ee values refer to the two C-3 epimers.

Table 3. Organocatalyzed Asymmetric Conjugate Addition of 1a to 3-Ylidene Oxindoles 2c−n[a]

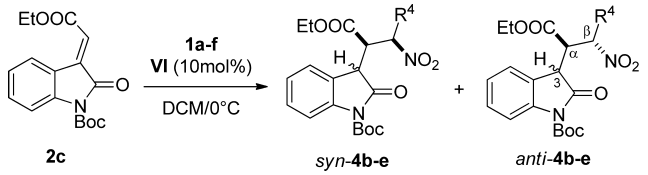


2c-n **3c-n**

entry	substrate	R^1	R^2	R^3	product	time (h)	yield (%)[b]	dr[c]	ee (%)[d]
1	**2c**	H	CO_2Et	H	**3c**	1	80	53/47	99/99
2	**2d**	5-Cl	CO_2Et	H	**3d**	3.5	83	60/40	>99/>99
3	**2e**	5-Br	CO_2Et	H	**3e**	3.5	72	53/47	>99/>99
4	**2f**	6-Cl	CO_2Et	H	**3f**	1.5	92	56/44	98/98
5	**2g**	7-Br	CO_2Et	H	**3g**	1	82	59/41	95/94
6	**2h**	5-OMe	CO_2Et	H	**3h**	1	89	55/45	>99/>99
7	**2i**	H	CO_2Bn	H	**3i**	2	72	55/45	>99/>99
8	**2j**	H	CO_2tBu	H	**3j**	2	99	57/43	>99/>99
9	**2k**	H	Ph	H	**3k**	2	52	59/41	60/64
10	**2l**	H	$p$$NO_2$Ph	H	**3l**	2	98	60/40	31/33
11	**2m**	H	tBu	H	**3m**	26	62	69/31	26/29
12	**2n**	H	CO_2Et	Me	**3n**	2	57	60/40	94/92

[a]Reaction conditions: **2** (0.1 mmol), **1a** (0.5 mmol), catalyst **VI** (5 mol %), DCM (0.15 mL), room temperature. [b]Yield of isolated product after flash chromatography. [c]Determined by ^{1}H NMR of the crude mixture. [d]Determined by CSP-HPLC of products **3**, isolated as a mixture of two C-3 epimers; ee values refer to the two C-3 epimers.

Table 4. Organocatalyzed Asymmetric Conjugate Addition of Nitroalkanes 1a−f to 3-Ylidene Oxindole 2c[a]



2c *syn*-**4b-e** *anti*-**4b-e**

entry	nitroalkane	product	time (h)	yield (%)[b]	*anti*/*syn*[c]	*ee anti* (%)[d]
1[e]	$MeNO_2$ (**1a**)	**3c**	1	80		99/99
2[e]	$EtNO_2$ (**1b**)	**4b**	2	78	76/24	97/98
3[f]	$EtNO_2$ (**1b**)	**4b**	48	73	99/1	>99/>99
4	$EtNO_2$ (**1b**)	**4b**	3	71	95/5	>99/>99
5	$n$$PrNO_2$ (**1c**)	**4c**	7	76	92/8	>99/>99
6	$MeO_2C(CH_2)_3NO_2$ (**1d**)	**4d**	4	83	91/9	>99/>99
7	$Ph(CH_2)_2NO_2$ (**1e**)	**4e**	4	72	90/10	>99/>99
8	$i$$PrNO_2$ (**1f**)	**4f**	144	traces		

[a]Reaction conditions: **2c** (0.1 mmol), **1** (0.5 mmol), catalyst **VI** (10 mol %), DCM (0.15 mL), 0 °C. [b]Yield of isolated product after flash chromatography. [c]Determined by CSP-HPLC of the crude mixture; the stereochemical notations *anti* and *syn* refer to the C_α−C_β relationship. [d]Determined by CSP-HPLC of the products, isolated as a mixture of two C-3 epimers; ee values refer to the two C-3 epimers. [e]Reaction performed at room temperature with 5 mol % of **VI**. [f]Reaction performed at −10 °C.

calculations performed by Papai,[19c] the bifunctional organocatalyst should simultaneously activate both Michael donor and acceptor, thus controlling the approach of the nitroalkane to the 3-ylidene oxindole. The oxindole reasonably interacts with the thiourea moiety via multiple hydrogen bonds, enhancing the electrophilicity of the reacting carbon center. Concurrently, the

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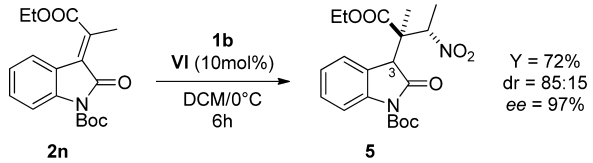
nitro compound coordinates to the tertiary amine group. The poor enantiocontrol observed when the methyleneindolinone was directly connected to an aryl or alkyl group suggests that the ester moiety affects the coordination between catalyst and substrate, enabling a high enantiocontrol. On the other hand, the interaction between the *N*-Boc carboxyl group and the catalyst, identified as crucial by many authors,[8j,9f,10e,f,k,n,11d,f] in our system seems to be present but not strictly necessary, as evidenced by the small differences in enantioselectivity recorded for substrates **2a**–**c** (Table 1, entries 1–3).

The substrate scope was also extended to the challenging construction of a quaternary stereocenter on the C_α position. For this purpose we applied our protocol to substrate **2n**, characterized by a tetrasubstituted exocyclic double bond (Table 3, entry 12). Once again, the reaction quickly provided the desired product with high ees for both diastereoisomers.

The next step in our investigation was to explore the use of higher nitroalkanes as Michael donors (Table 4), with the aim of introducing a further stereocenter and approaching the structural complexity of bioactive oxindoles.

We first applied the same conditions optimized for nitromethane **1a** (Table 4, entry 1). Nitroethane **1b** quickly provided the desired product **4b** in good yield and excellent stereocontrol at C_α, but with modest control of the C_β stereochemistry (entry 2). We tried to improve the dr by lowering the temperature, and pleasingly, the diastereocontrol at −10 °C was almost complete (entry 3). However, the reaction time was much longer (48 h), so that the best trade-off between reactivity and stereoselectivity was reached by employing 10 mol % of catalyst at 0 °C. After 3 h **4b** was obtained in good yield and dr and high ees for each diastereoisomer (entry 4). The protocol was successfully applied to nitroalkanes **1c**–**e** (entries 5–7). Only the isopropyl derivative **1f** did not afford the corresponding product (entry 8); this was probably due to the great steric compression at the α-nitro position. Data presented in Table 4 showed that the configurations of the two stereocenters directly generated in the conjugate addition were highly defined, while the C-3 configuration was, as usual, out of control. With the aim of introducing a quaternary and two tertiary adjacent stereocenters on the oxindole scaffold, we extended the addition of nitroethane **1b** to substrate **2n** (Scheme 3).

Scheme 3. Organocatalytic Protocol Employed To Stereoselectively Introduce a Quaternary and Two Tertiary Adjacent Stereocenters



The adduct **5** was obtained in good yield and high ee, and surprisingly, in this case the two C-3 epimers were not equally present (dr = 85/15). A possible explanation could be that the steric crowding and the substituent distribution on the adjacent stereocenters partially affect the C-3 configuration.

Summarizing the first part of this study, we developed an asymmetric organocatalytic protocol for the conjugate addition of nitroalkanes to 3-ylidene oxindoles, which efficiently provided substituted β-nitro indolin-2-ones in good yields and excellent enantioselectivities. Indeed, up to three stereocenters were generated one pot, two of them with high stereocontrol. Although it was not possible to control the absolute configuration of the third stereocenter, this limitation can be turned into an opportunity if we react the β-nitro oxindole **4** with an electrophile, with the aim of building up an all-carbon C-3 quaternary stereocenter increasing the structural complexity (Scheme 2, eq 1). With respect to the previously reported strategies, that employ simple C-3 racemic substrates[4a,c,e,5,10] (Scheme 1, eq 2a), our approach consists of reacting a pair of diastereoisomers (Scheme 1, eq 3). In this perspective, the β-nitro indolin-2-one scaffold **4** could represent a useful precursor for the asymmetric synthesis of 3,3′-disubstituted oxindoles with more substitution variants.

The first attempts were made by exploiting *N*-phenylmaleimide,[20] 1,1-bis(benzenesulfonyl)ethylene[21] and *trans*-β-nitrostyrene[22] as electrophiles, in the presence of the same thiourea catalyst used for the preliminary Michael addition. As shown in Scheme 4, the reaction with *N*-phenylmaleimide proceeded smoothly, affording product **6** as a single stereoisomer in good yield. In this one-pot three-component tandem reaction four contiguous stereocenters, including the desired C-3 all-carbon quaternary center, were enantioselectively generated.

To introduce structural diversity, the reactivity of **4b** was also tested in the Michael addition to 1,1-bis(benzenesulfonyl)-ethylene (Scheme 4). Compound **7**, featuring three adjacent stereocenters, was efficiently isolated with excellent stereoenrichment. With regard to the organocatalyzed conjugate addition of 3-substituted racemic oxindole derivatives to vinyl sulfones, it is known that good stereocontrol is possible only if an aryl substituent on C-3 is present, while 3-alkyl oxindoles generally afford the corresponding adducts in low yields and poor enantioselectivity. For this reason, Lu and co-workers[21a] and Kim and co-workers[21b] were forced to develop specifically modified organocatalysts. In our case, thanks to the matched induction of pre-existing stereocenters and catalyst, the asymmetric Michael reaction smoothly proceeded on 3-alkyl oxindole **4b** with the readily available Takemoto catalyst **VI**.

The last application of the hydrogen-bond catalysis involved the addition of **4b** to *trans*-β-nitrostyrene (Scheme 5), further confirming the versatility of the β-nitro indolin-2-one scaffold as a synthetic precursor of optically active 3,3′-disubstituted oxindoles.

One of the advantages of the proposed one-pot tandem reactions was that a single catalyst sequentially promoted two different transformations, so that the addition of other catalysts was not necessary. However, to further expand the opportunities of structural diversification, we explored a second activation mode employing covalent amino catalysis for the reaction of **4b** with 2-cyclohexen-1-one[10p,11a] and with crotonaldehyde.[8a,c,d,10j,11c,d] As depicted in Scheme 6, the thiourea **VI** was easily removed by means of an acidic workup, allowing us to carry out the subsequent Michael reaction directly on the crude reaction mixture containing **4b**.

Primary amine **X** and secondary amine **XI** represent the matched catalysts for the addition of *anti*-**4b** to cyclohexenone and crotonaldehyde, respectively, affording the corresponding products **9** and **10** in good yields. Once again, 3,3′-disubstituted oxindoles bearing four contiguous stereocenters were obtained with good to excellent stereocontrol.

A notable synthetic application of the β-nitro oxindole scaffold lies in its easy conversion to the corresponding β-amino motif recognized in many bioactive compounds.[1−3] As depicted in Scheme 7, on reduction with Raney nickel of the β-nitro indolin-2-one **4b**, we quantitatively obtained the expected β-amino indolin-2-one **11**.

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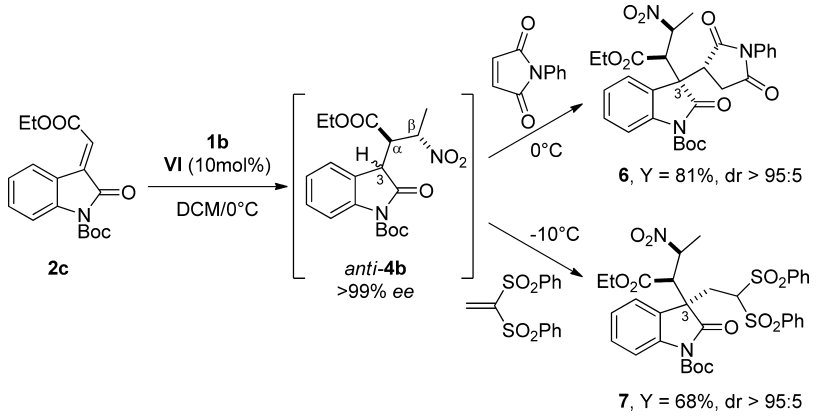
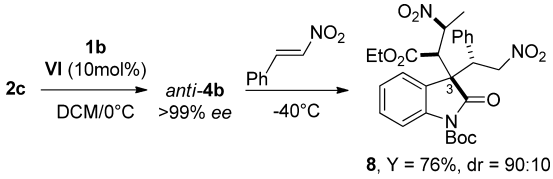
Scheme 4. One-Pot Three-Component Tandem Reactions To Access 3,3′-Disubstituted Oxindoles 6 and 7

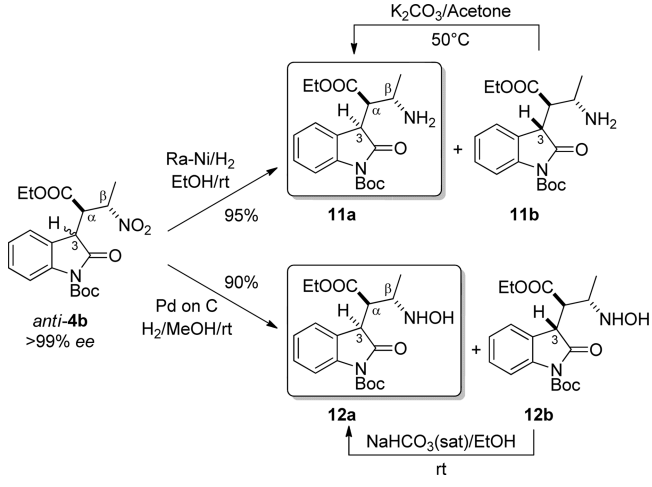


Scheme 5. One-Pot Three-Component Tandem Reaction To Access 3,3′-Disubstituted Oxindole 8



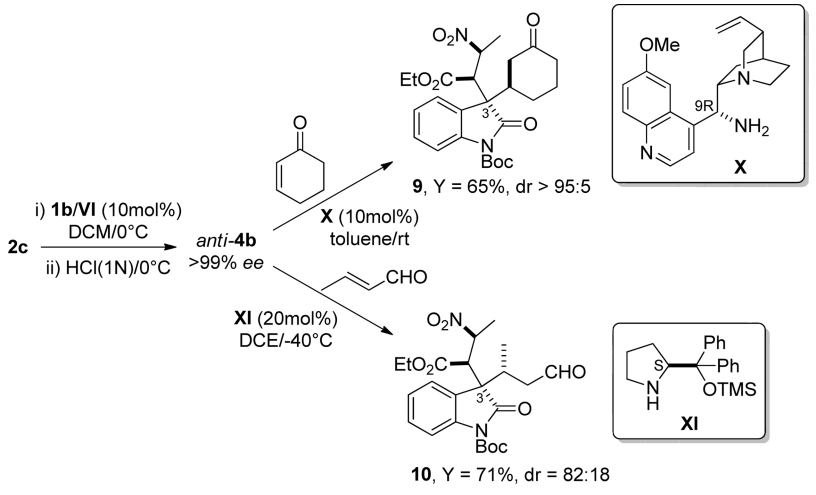
Looking for the best reaction conditions, we tried also palladium on carbon as a reducing agent and, interestingly, the pair of observed products was different from those obtained using Raney nickel. A careful analysis of the HPLC-MS and NMR spectra allowed us to establish that the palladium catalyst partially reduces the *β*-nitro oxindole **4b** to the corresponding *β*-hydroxylamino oxindole **12**[23] (Scheme 7). As expected, the *β*-amino and the *β*-hydroxylamino derivatives were both isolated as mixtures of two C-3 epimers (**11a**,**b** and **12a**,**b**, respectively) but, interestingly, when subjected to basic conditions they converged to a single stereoisomer (Scheme 7). As previously mentioned about compound **5**, the C-3 configuration could be affected by the stereochemical features and the ability to form specific interactions of the substituents on C_α and C_β. In this case, the greater thermodynamic stability of **11a** and **12a** acts as a driving force in the base-promoted stereoconvergent C-3 epimerization.

Scheme 7. Reducing Agent Dependent Transformations of *β*-Nitro Oxindole 4b into *β*-Amino 11 and *β*-Hydroxylamino 12 Oxindoles. Stereoconvergent Base-Promoted C-3 Epimerization of *β*-Amino and *β*-Hydroxylamino Derivatives



At last we remark the usefulness of the asymmetric organocatalytic conjugate addition of nitroalkanes to 3-ylidene oxindoles reported here in the synthesis of enantioenriched oxindole and indoline derivatives, potentially exploitable in drug discovery. For example, the optically active conjugate adduct

Scheme 6. Sequential Synthesis of 3,3′-Disubstituted Oxindoles 9 and 10



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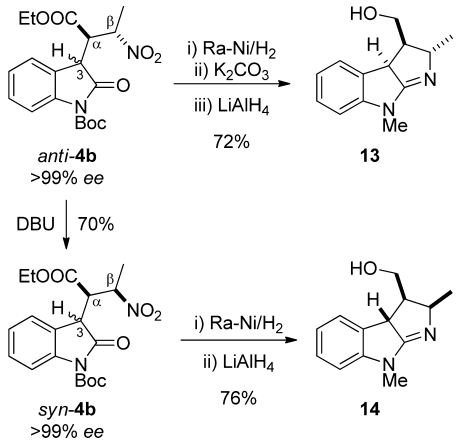
anti-**4b** (>99% ee) was first reduced and then cyclized to compound **13**, featuring a core structure similar to those of many important natural products[24] (Scheme 8). The absolute configuration of compound **13** has been determined by theoretical calculation of its electronic circular dichroism (ECD) spectrum and of its optical rotation (OR), using the TD-DFT method (see the Supporting Information).

Scheme 8. Synthetic Elaborations on the Optically Active Conjugate Adduct *anti*-4b To Obtain the Stereochemically Different Compounds 13 and 14, Featuring a Natural Core Structure



The possibility of creating stereochemically different scaffolds starting from the same substrate could be synthetically very useful, providing a platform of diastereomeric derivatives to better evaluate the effect of relative stereochemistry on bioactivity. With this aim, exploiting the acidity on the C_β position, we subjected *anti*-**4b** to basic conditions (1,5-diazabicyclo[5.4.0]undec-5-ene, DBU, 30 mol %) and *syn*-**4b** was isolated in good yield without compromising the optical purity. The previously described reductive protocol[25] allowed us to obtain product **14**, characterized by a relative stereochemistry different from that of compound **13**. Thus, the C_α absolute configuration, controlled by the chiral thiourea during the conjugate addition, is the only one that remains unchanged, while the stereochemistry at the other centers can be manipulated by means of stereoconvergent transformations, depending on the desired target molecule.

CONCLUSION

Even though asymmetric processes applied to indoles, oxindoles, and isatins seem to represent a mature field in organocatalysis, we demonstrated that still a number of useful reactions and applications can be disclosed. We carefully examined the Michael addition of nitroalkanes to 3-ylidene oxindoles and found optimized conditions to perfectly control the stereochemistry at C_α and C_β centers. Under our reaction conditions we had no chance to stereodefine the C-3 position; however, when the generated intermediate enolate was trapped with a second Michael acceptor, an all-carbon quaternary stereocenter was formed in a perfectly defined configuration. The conversion of the β-nitro oxindole adduct into the corresponding β-amino derivative disclosed intriguing and synthetically useful transformations, such as stereoconvergent processes and stereoselective base-promoted isomerizations. Considering the number of substrates examined and the number of synthetic transformations they were subjected to, we believe to have demonstrated the synthetic value of the developed asymmetric Michael addition of nitroalkanes to 3-ylidene oxindoles, complementary to the most widely studied reactions present in the literature.

EXPERIMENTAL SECTION

Materials. All of the chemicals were used as received. Catalysts **I**–**V** were known and prepared according to the literature procedures.[26] Compounds **2a**,[27] **2b,c**,[28] **2d**–**f,h**,[11f] **2i**,[9f] **2j,k**,[9a,d] **2l**,[9b] and **1e**[29] were known and prepared according to the literature procedures.

Characterization of Compounds. ^{1}H and ^{13}C NMR spectra were recorded on a 200 or 400 NMR instrument with a 5 mm probe. All chemical shifts have been quoted relative to deuterated solvent signals; chemical shifts (δ) are reported in ppm, and coupling constants (J) are reported in Hz; HPLC-MS analysis was performed using an HPLC system coupled with a single-quadrupole mass spectrometer. A ZOBRAX-Eclipse XDB-C8 column was employed for the chromatographic separation: mobile phase H_2O/CH_3CN, gradient from 30% to 80% of CH_3CN in 8 min, 80% of CH_3CN until 25 min, 0.4 mL min^{-1}. Mass spectrometric detection was performed in full-scan mode from m/z 50 to 2600: scan time 0.1 s in positive ion mode, ESI spray voltage 4500 V, nitrogen gas 35 psi, drying gas flow 11.5 mL min^{-1}, fragmentor voltage 20 V. CSP-HPLC analyses were performed using hexane/2-propanol (*n*-Hex/IPA) mixtures. Flash chromatography was carried out using Merck silica gel 60 (230–400 mesh particle size). Thin-layer chromatography was performed on Merck 60 F254. The $[\alpha]_D^{25}$ values and the *major* enantiomers in the following characterization have been defined with respect to the products obtained with catalyst **VI**.

Synthesis of (*E*)-*tert*-Butyl 7-Bromo-3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate (2g). Ethyl 2-(triphenylphosphoranylidene)acetate (1.2 mmol) was added to a solution of 7-bromoindoline-2,3-dione (1 mmol, 226 mg) in DCM (4 mL). The reaction mixture was stirred at room temperature overnight. After the reaction was complete, the solvent was removed under reduced pressure. The crude mixture was dissolved in THF (5 mL), DMAP (4-dimethylaminopyridine, 5 mol %) was added to the solution, and finally, Boc_2O (di-*tert*-butyl dicarbonate, 1.1 mmol) was added. The reaction mixture was stirred at room temperature for 1 h. Then the solvent was removed under reduced pressure and the product was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 9/1): 95% yield (376 mg), crystalline solid (mp 73–77 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.66 (dd, J = 7.9 and 1.1 Hz, 1H), 7.59 (dd, J = 8.1 and 1.1 Hz, 1H), 7.08 (t, J = 8.0 Hz, 1H), 6.94 (s, 1H), 4.34 (q, J = 7.1 Hz, 2H), 1.66 (s, 9H), 1.38 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 27.7, 61.5, 85.8, 106.7, 123.4, 124.6, 125.6, 127.5, 136.2, 137.1, 140.8, 147.6, 164.9, 166.3; HPLC-MS (ESI) t_r = 12.7 min; $[M + Na]^+$ 418.2 m/z, $[2M + Na]^+$ 813.2 m/z, 817.2 m/z. Anal. Calcd for $C_{17}H_{18}BrNO_5$ (395.04): C, 51.53; H, 4.58; N, 3.53. Found: C, 51.37; H, 4.56; N, 3.54.

Synthesis of (*E*)-*tert*-Butyl 3-(2,2-Dimethylpropylidene)-2-oxoindoline-1-carboxylate (2m). Pivalaldehyde (1.2 mmol) was added to a solution of indolin-2-one (1 mmol, 133 mg) in EtOH (5 mL), finally piperidine (10 mol %) was added. The reaction was refluxed for 1.5 h, then it was cooled to room temperature and the solvent was removed under reduced pressure. The product was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 8/2). (*E*)-3-(2,2-Dimethylpropylidene)indolin-2-one was dissolved in THF (5 mL), and then DMAP (5 mol %) was added and finally Boc_2O (1.1 mmol). The reaction mixture was stirred at room temperature for 1 h. After the reaction was complete, the solvent was removed under reduced pressure and the product was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 9/1): 97% yield (292 mg); crystalline solid (mp 82–86 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 7.8 Hz, 1H), 7.78–7.71 (m, 1H), 7.36–7.29 (m, 1H), 7.25 (s, 1H), 7.17 (td, J = 7.7 and 1.2 Hz, 1H), 1.65 (s, 9H), 1.39 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 28.1, 29.1, 32.7, 84.0, 115.0, 120.9, 123.5, 125.5, 126.0, 128.9, 140.0, 149.3, 154.3, 167.0; HPLC-MS (ESI) t_r = 13.4 min; $[2M + Na]^+$ = 625.4 m/z. Anal. Calcd for $C_{18}H_{23}NO_3$ (301.17): C, 71.73; H, 7.69; N, 4.65. Found: C, 71.61; H, 7.71; N, 4.65.

Synthesis of (*E*)-*tert*-Butyl 3-(1-Ethoxy-1-oxopropan-2-ylidene)-2-oxoindoline-1-carboxylate (2n). DMAP (5 mol %) was added to a solution of indoline-2,3-dione (1 mmol, 147 mg) in THF

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(5 mL); then Boc_2O (1.1 mmol) was added. The reaction mixture was stirred at room temperature for 1 h. After the reaction was complete, the solvent was removed under reduced pressure. The crude mixture was dissolved in DCM (4 mL), and ethyl 2-(triphenylphosphoranylidene)-propanoate (1.2 mmol) was added. The reaction mixture was stirred at room temperature overnight. Then the solvent was removed under reduced pressure and the product was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 9/1): 50% yield (166 mg), gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (d, J = 8.7 Hz, 1H), 7.36−7.29 (m, 2H), 7.09 (t, J = 7.7 Hz, 1H), 4.43 (q, J = 7.1 Hz, 2H), 2.63 (s, 3H), 1.66 (s, 9H), 1.39 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 17.1, 28.1, 30.9, 62.0, 84.4, 114.9, 120.7, 122.0, 123.4, 123.9, 129.9, 138.8, 141.8, 149.2, 165.7, 169.2; HPLC-MS (ESI) t_r = 11.7 min; $[M + Na]^+$ = 354.2 m/z, $[2M + Na]^+$ = 685.5 m/z. Anal. Calcd for $C_{18}H_{21}NO_5$ (331.14): C, 65.24; H, 6.39; N, 4.23. Found: C, 65.22; H, 6.37; N, 4.22.

General Procedure for the Organocatalyzed Michael Addition of Nitroalkanes 1 to 3-Ylidene Oxindoles 2. The 3-ylidene oxindole (0.1 mmol) was added to a solution of catalyst (5 or 10 mol %) in DCM (0.15 mL), and then nitroalkane (0.5 mmol) was added at room temperature or at 0 °C. The mixture was stirred at the same temperature, and the conversion was monitored by TLC and ^{1}H NMR. The crude mixture of the reactions performed at room temperature was directly purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 85/15). The crude mixture of the reactions performed at 0 °C was quenched at the same temperature with 2 mL of HCl (1 N) and extracted with DCM (3 × 2 mL). The organic phases were collected and dried over Na_2SO_4, the solvent was evaporated under reduced pressure without heating, and the product was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 85/15). Before CSP-HPLC analysis, the purified product (0.04 mmol) (and, when necessary, the crude reaction mixture) was deprotected using 18 equiv of trifluoroacetic acid (TFA) in 0.4 mL of DCM. After 45 min the reaction was quenched with 2 mL of a 0.1 M solution of phosphate buffer (pH 7) and the aqueous phase was extracted with DCM (2 × 2 mL). The organic phases were collected and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the corresponding N-deprotected β-nitro oxindole was obtained pure and directly injected into CSP-HPLC.

*3-((R)-1-Ethoxy-3-nitro-1-oxopropan-2-yl)-2-oxoindoline (**3a**):* mixture of two diastereoisomers; 85% yield (24 mg), oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (bs, 2H), 7.34−7.20 (m, 3H), 7.17 (d, J = 7.5 Hz, 1H), 7.12−7.01 (m, 2H), 6.91 (d, J = 7.8 Hz, 2H), 4.99 (dd, J = 14.5 and 9.4 Hz, 1H), 4.78 (dd, J = 14.8 and 8.9 Hz, 1H), 4.46 (m, 2H), 4.29−4.14 (m, 4H), 4.14−4.07 (m, 1H), 4.04 (m, 1H), 3.99−3.91 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H), 1.17 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 13.9, 43.0, 43.3, 45.0, 45.1, 62.1, 62.2, 72.0, 72.3, 110.3, 122.9, 123.0, 124.3, 124.4, 124.8, 125.0, 129.2, 129.3, 141.3, 141.6, 169.1, 169.8, 176.5, 176.8; HPLC-MS (ESI) t_r = 6.4 min, 6.8 min; $[M + H]^+$ = 279.2 m/z, $[M + Na]^+$ = 301.2 m/z. Anal. Calcd for $C_{13}H_{14}N_2O_5$ (278.09): C, 56.11; H, 5.07; N, 10.07. Found: C, 55.91; H, 5.09; N, 10.04. CSP-HPLC: OJ 90/10 n-Hex/IPA for 10 min, then up to 80/20 in 20 min, 80/20 up to 60 min; flow rate 0.5 mL/min at 40 °C; λ 214 nm; t_r(isomer A) = 38.5 min (major), 44.8 min (minor); t_r(isomer B) = 42.7 min (major), 53.8 min (minor).

*(2R)-Ethyl 2-(1-benzyl-2-oxoindolin-3-yl)-3-nitropropanoate (**3b**):* mixture of two diastereoisomers; 86% yield (32 mg), gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39−7.16 (m, 14H), 7.10−7.01 (m, 2H), 6.84−6.72 (m, 2H), 5.03−4.88 (m, 5H), 4.80 (dd, J = 14.8 and 8.9 Hz, 1H), 4.52−4.37 (m, 2H), 4.24−4.04 (m, 6H), 4.01 (d, J = 3.7 Hz, 2H), 1.17 (t, J = 7.1 Hz, 3H), 1.08 (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 13.8, 43.2, 43.4, 44.09, 44.11, 44.5, 44.6, 62.0, 62.1, 72.10, 72.41, 109.5, 122.9, 123.0, 124.0, 124.1, 124.3, 124.5, 127.4, 127.5, 127.88, 127.91, 128.86, 128.87, 129.0, 129.2, 135.40, 135.42, 143.4, 143.6, 169.2, 169.7, 174.4, 174.6; HPLC-MS (ESI) t_r = 9.5 min, 9.8 min; $[M + H]^+$ = 369.2 m/z, $[M + Na]^+$ = 391.2 m/z. Anal. Calcd for $C_{20}H_{20}N_2O_5$ (368.14): C, 65.21; H, 5.47; N, 7.60. Found: C, 65.06; H, 5.47; N, 7.61. CSP-HPLC: IC 90/10 n-Hex/IPA for 10 min, then up to 85/15 in 5 min, 85:15 up to 80 min; flow rate 0.5 mL/min at room temperature; λ 254 nm. t_r(isomer A) = 56.1 min (major), 71.0 min (minor); t_r(isomer B) = 61.2 min (major), 73.6 min (minor).

*tert-Butyl 3-((R)-1-ethoxy-3-nitro-1-oxopropan-2-yl)-2-oxoindoline-1-carboxylate (**3c**):* mixture of two diastereoisomers; 80% yield (30 mg), oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (dd, J = 8.4 and 2.8 Hz, 2H), 7.41−7.33 (m, 2H), 7.29−7.14 (m, 4H), 5.01 (dd, J = 14.4 and 9.3 Hz, 1H), 4.84 (dd, J = 14.9 and 8.1 Hz, 1H), 4.64 (dd, J = 14.8 and 5.8 Hz, 1H), 4.40 (dd, J = 14.4 and 5.0 Hz, 1H), 4.23−4.06 (m, 6H), 4.04 (d, J = 3.8 Hz, 1H), 3.99 (d, J = 3.1 Hz, 1H), 1.65 (s, 18H), 1.18 (t, J = 7.1 Hz, 3H), 1.13 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 13.8, 28.0, 43.7, 43.9, 45.0, 45.4, 62.2, 62.3, 72.3, 72.4, 84.9, 85.0, 115.3, 115.4, 123.2, 123.5, 123.6, 123.7, 124.7, 124.8, 129.2, 129.5, 140.3, 140.6, 148.77, 148.76, 168.7, 169.2, 172.7, 173.4; HPLC-MS (ESI) t_r = 9.9 min, 10.0 min; $[M + Na]^+$ = 401.3 m/z. Anal. Calcd for $C_{18}H_{22}N_2O_7$ (378.14): C, 57.14; H, 5.86; N, 7.40. Found: C, 57.02; H, 5.85; N, 7.39.

3-((R)-1-Ethoxy-3-nitro-1-oxopropan-2-yl)-2-oxoindoline: mixture of two diastereoisomers; CSP-HPLC: OJ 90/10 n-Hex/IPA for 10 min, then up to 80/20 in 20 min, 80/20 up to 70 min; flow rate 0.5 mL/min at room temperature; λ 214 nm; t_r(isomer A) = 43.2 min (major), 51.8 min (minor); t_r(isomer B) = 49.5 min (major), 63.9 min (minor).

*tert-Butyl 5-chloro-3-((R)-1-ethoxy-3-nitro-1-oxopropan-2-yl)-2-oxoindoline-1-carboxylate (**3d**):* mixture of two diastereoisomers; 83% yield (34 mg), oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 5.1 Hz, 1H), 7.83 (d, J = 5.2 Hz, 1H), 7.38−7.31 (m, 2H), 7.24−7.20 (m, 2H), 5.00 (dd, J = 14.4 and 9.0 Hz, 1H), 4.91 (dd, J = 14.8 and 7.3 Hz, 1H), 4.78 (dd, J = 14.8 and 6.6 Hz, 1H), 4.46 (dd, J = 14.4 and 5.2 Hz, 1H), 4.22−4.03 (m, 6H), 4.00 (d, J = 4.3 Hz, 1H), 3.93 (d, J = 3.0 Hz, 1H), 1.64 (s, 18H), 1.22−1.09 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.68, 13.73, 28.0, 43.7, 44.0, 44.7, 45.2, 62.4, 62.5, 72.2, 72.6, 85.2, 85.3, 116.6, 116.7, 123.7, 123.9, 125.1, 125.8, 129.2, 129.5, 130.2, 130.3, 138.9, 139.1, 148.6, 168.4, 168.6, 171.9, 172.8; HPLC-MS (ESI) t_r = 10.7 min; $[M + Na]^+$ = 435.2, 437.3 m/z, $[M + K]^+$ = 451.2 m/z, $[2M + Na]^+$ = 847.4 m/z. Anal. Calcd for $C_{18}H_{21}ClN_2O_7$ (412.10): C, 52.37; H, 5.13; N, 6.79. Found: C, 52.21; H, 5.14; N, 6.78.

5-Chloro-3-((R)-1-ethoxy-3-nitro-1-oxopropan-2-yl)-2-oxoindoline: mixture of two diastereoisomers, gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (bs, 2H), 7.52−7.48 (m, 1H), 7.33−7.16 (m, 3H), 6.92−6.76 (m, 2H), 4.99 (dd, J = 14.4 and 9.0 Hz, 1H), 4.84 (dd, J = 14.7 and 8.2 Hz, 1H), 4.65−4.55 (m, 1H), 4.52 (dd, J = 14.5 and 4.9 Hz, 1H), 4.40 (m, 1H), 4.27−4.16 (m, 3H), 4.12−4.05 (m, 2H), 4.02−3.87 (m, 2H), 1.31−1.15 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 13.9, 43.1, 43.3, 44.8, 44.9, 62.3, 62.4, 72.1, 72.2, 111.0, 111.1, 124.5, 124.7, 124.9, 124.9, 126.8, 128.0, 128.4, 129.1, 129.3, 129.5, 139.7, 139.9, 168.9, 169.3, 176.0; HPLC-MS (ESI) t_r = 7.5 min, 7.6 min; $[M + H]^+$= 313.1 m/z, $[M + Na]^+$= 335.1 m/z. Anal. Calcd for $C_{13}H_{13}ClN_2O_5$ (312.05): C, 49.93; H, 4.19; N, 8.96. Found: C, 49.89; H, 4.20; N, 8.94. CSP-HPLC: IC 90/10 n-Hex/IPA up to 50 min; flow rate 0.6 mL/min at room temperature; λ 214 nm; t_r(isomer A) = 31.4 min (major), 39.7 min (minor); t_r(isomer B) = 44.2 min (minor), 45.9 min (major).

*tertButyl 5-bromo-3-((R)-1-ethoxy-3-nitro-1-oxopropan-2-yl)-2-oxoindoline-1-carboxylate (**3e**):* mixture of two diastereoisomers; 72% yield (33 mg), oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82−7.76 (m, 2H), 7.53−7.45 (m, 2H), 7.40−7.32 (m, 2H), 5.00 (dd, J = 14.4 and 9.0 Hz, 1H), 4.91 (dd, J = 14.8 and 7.3 Hz, 1H), 4.80 (dd, J = 14.8 and 6.6 Hz, 1H), 4.46 (dd, J = 14.5 and 5.1 Hz, 1H), 4.24−4.02 (m, 6H), 4.00 (d, J = 4.3 Hz, 1H), 3.93 (d, J = 3.0 Hz, 1H), 1.64 (s, 18H), 1.22−1.09 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 13.7, 28.0, 43.8, 44.1, 44.7, 45.1, 62.4, 62.5, 72.2, 72.6, 85.2, 85.4, 117.0, 117.0, 117.6, 117.7, 125.5, 126.2, 126.5, 126.7, 132.1, 132.5, 139.4, 139.6, 148.6, 168.4, 168.6, 171.8, 172.7; HPLC-MS (ESI) t_r = 10.9 min; $[M + Na]^+$= 479.2, 481.1 m/z. Anal. Calcd for $C_{18}H_{21}BrN_2O_7$ (456.05): C, 47.28; H, 4.63; N, 6.13. Found: C, 47.13; H, 4.61; N, 6.11.

5-Bromo-3-((R)-1-ethoxy-3-nitro-1-oxopropan-2-yl)-2-oxoindoline: mixture of two diastereoisomers, gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (bs, 2H), 7.45−7.38 (m, 2H), 7.38−7.29 (m, 2H), 6.84−6.76 (m, 2H), 4.99 (dd, J = 14.5 and 8.8 Hz, 1H), 4.84 (dd, J = 14.8 and 8.1 Hz, 1H), 4.62 (dd, J = 14.8 and 5.7 Hz, 1H), 4.52 (dd, J = 14.5 and 4.8 Hz, 1H), 4.26−4.18 (m, 4H), 4.12−4.04 (m, 1H), 4.00−3.89 (m, 3H), 1.31−1.14 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 13.9, 43.2, 43.3, 44.7, 44.8, 62.3, 62.4, 72.17, 72.23, 111.4, 111.5, 115.5, 127.2, 127.3, 127.6, 127.7, 132.0, 132.2, 140.2, 140.4, 168.9, 169.2, 175.2, 175.7; HPLC-MS (ESI) t_r = 7.7 min; $[M + H]^+$ = 357.1, 359.1 m/z, $[M + Na]^+$ = 379.1, 381.0 m/z. Anal. Calcd for $C_{13}H_{13}BrN_2O_5$ (356.00): C, 43.72; H,

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3.67; N, 7.84. Found: C, 43.69; H, 3.68; N, 7.83. CSP-HPLC: IC 90/10 *n*-Hex/IPA for 10 min, then up to 80/20 in 10 min, 80/20 for 15 min, then up to 75/25 in 15 min, 75/25 up to 40 min; flow rate 0.5 mL/min at room temperature; λ 214 nm; t_r(isomer A) = 27.7 min (major), 31.3 min (minor); t_r(isomer B) = 32.4 min (major), 33.0 min (minor).

*tert-Butyl 6-chloro-3-((R)-1-ethoxy-3-nitro-1-oxopropan-2-yl)-2-oxoindoline-1-carboxylate (**3f**):* mixture of two diastereoisomers; 92% yield (38 mg), oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98−7.92 (m, 2H), 7.22−7.12 (m, 4H), 5.00 (dd, J = 14.3 and 9.0 Hz, 1H), 4.87 (dd, J = 14.8 and 7.5 Hz, 1H), 4.74 (dd, J = 14.8 and 6.4 Hz, 1H), 4.44 (dd, J = 14.4 and 5.3 Hz, 1H), 4.21−4.04 (m, 6H), 3.98 (d, J = 3.9 Hz, 1H), 3.92 (d, J = 2.7 Hz, 1H), 1.65 (s, 18H), 1.22−1.11 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.7, 13.8, 28.0, 43.8, 44.0, 44.6, 45.0, 62.3, 62.4, 72.3, 72.5, 85.4, 85.5, 116.16, 116.23, 121.7, 122.3, 124.3, 124.5, 124.7, 124.8, 135.1, 135.4, 141.3, 141.5, 148.5, 168.4, 168.8, 172.2, 173.0; HPLC-MS (ESI) t_r = 10.9 min; $[M + Na]^+$ = 435.2 m/z, $[2M+Na]^+$ = 847.4 m/z. Anal. Calcd for $C_{18}H_{21}ClN_2O_7$ (412.10): C, 52.37; H, 5.13; N, 6.79. Found: C, 52.16; H, 5.13; N, 6.78.

6-Chloro-3-((R)-1-ethoxy-3-nitro-1-oxopropan-2-yl)-2-oxoindoline: mixture of two diastereoisomers, gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (bs, 2H), 7.19−7.02 (m, 4H), 6.95 (s, 2H), 4.99 (dd, J = 14.4 and 9.0 Hz, 1H), 4.81 (dd, J = 14.7 and 8.3 Hz, 1H), 4.57 (dd, J = 14.7 and 5.5 Hz, 1H), 4.49 (dd, J = 14.4 and 5.1 Hz, 1H), 4.26−4.11 (m, 4H), 4.08 (ddd, J = 8.6 and 5.5 and 3.4 Hz, 1H), 4.01 (m, 1H), 3.93−3.87 (m, 2H), 1.23 (t, J = 7.1 Hz, 3H), 1.18 (t, J = 7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.8, 13.9, 43.1, 43.3, 44.5, 44.6, 62.26, 62.34, 72.1, 72.3, 110.9, 122.9, 123.0, 123.37, 123.42, 125.28, 125.32, 135.0, 135.2, 142.4, 168.9, 169.5, 176.4, 176.7; HPLC-MS (ESI) t_r = 7.3 min, 7.7 min; $[M + Na]^+$ = 335.1 m/z. Anal. Calcd for $C_{13}H_{13}ClN_2O_5$ (312.05): C, 49.93; H, 4.19; N, 8.96. Found: C, 49.77; H, 4.18; N, 8.93. CSP-HPLC: IC 90/10 *n*-Hex/IPA for 35 min, then up to 80/20 in 15 min, 80/20 for 10 min, then up to 70/30 in 5 min, 70/30 for 5 min, then up to 1/1 in 2 min, 1/1 up to 73 min; flow rate 0.6 mL/min at room temperature; λ 254 nm; t_r(isomer A) = 33.4 min (major), 52.7 min (minor); t_r(isomer B) = 44.1 min (minor), 68.4 min (major).

*tert-Butyl 7-bromo-3-((R)-1-ethoxy-3-nitro-1-oxopropan-2-yl)-2-oxoindoline-1-carboxylate (**3g**):* mixture of two diastereoisomers; 82% yield (37 mg), oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56−7.47 (m, 2H), 7.22−7.16 (m, 2H), 7.05 (t, J = 7.8 Hz, 2H), 5.01 (dd, J = 14.4 and 9.0 Hz, 1H), 4.88 (dd, J = 14.9 and 7.5 Hz, 1H), 4.74 (dd, J = 14.9 and 6.4 Hz, 1H), 4.44 (dd, J = 14.4 and 5.1 Hz, 1H), 4.20−4.05 (m, 6H), 4.04 (d, J = 3.9 Hz, 1H), 3.99 (d, J = 3.2 Hz, 1H), 1.66 (s, 9H), 1.65 (s, 9H), 1.15 (t, J = 7.6 Hz, 3H), 1.12 (t, J = 7.6 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.6, 13.7, 27.7, 43.7, 44.0, 45.2, 45.6, 62.5, 72.3, 72.4, 86.0, 86.1, 106.5, 106.6, 122.6, 122.8, 125.49, 125.54, 127.0, 127.6, 134.0, 134.3, 139.3, 139.5, 147.5, 168.4, 168.6, 173.0, 173.7; HPLC-MS (ESI) t_r = 10.5 min; $[M + Na]^+$ = 479.1, 481.2 m/z. Anal. Calcd for $C_{18}H_{21}BrN_2O_7$ (456.05): C, 47.28; H, 4.63; N, 6.13. Found: C, 47.13; H, 4.64; N, 6.14.

7-Bromo-3-((R)-1-ethoxy-3-nitro-1-oxopropan-2-yl)-2-oxoindoline: mixture of two diastereoisomers, gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (bs, 2H), 7.43 (d, J = 3.7 Hz, 1H), 7.41 (d, J = 3.7 Hz, 1H), 7.17 (d, J = 7.4 Hz, 1H), 7.13 (d, J = 7.7 Hz, 1H), 7.00−6.93 (m, 2H), 5.01 (dd, J = 14.4 and 9.0 Hz, 1H), 4.81 (dd, J = 14.8 and 8.4 Hz, 1H), 4.60 (dd, J = 14.8 and 5.5 Hz, 1H), 4.49 (dd, J = 14.5 and 4.6 Hz, 1H), 4.26−3.99 (m, 8H), 1.21 (t, J = 7.1 Hz, 3H), 1.15 (t, J = 7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.7, 13.8, 43.2, 43.3, 46.0, 46.2, 62.2, 62.3, 72.1, 72.4, 103.2, 103.3, 123.1, 124.1, 126.30, 126.34, 131.8, 132.0, 140.8, 141.04, 168.8, 169.3, 174.8, 175.2; HPLC-MS (ESI) t_r = 7.3 min, 7.6 min; $[M + H]^+$ = 357.2, 359.1 m/z, $[M + Na]^+$ = 379.1, 381.0 m/z. Anal. Calcd for $C_{13}H_{13}BrN_2O_5$ (356.00): C, 43.72; H, 3.67; N, 7.84. Found: C, 43.71; H, 3.68; N, 7.81. CSP-HPLC: IC 85:15 *n*-Hex/IPA for 15 min, then up to 80/20 in 10 min, 80/20 for 10 min, then up to 70/30 in 10 min, 70/30 up to 70 min; flow rate 0.5 mL/min at 14 °C; λ 214 nm; t_r(isomer A) = 48.4 min (major), 50.7 min (minor); t_r(isomer B) = 57.4 min (major), 66.1 min (minor).

*tert-Butyl 3-((R)-1-ethoxy-3-nitro-1-oxopropan-2-yl)-5-methoxy-2-oxoindoline-1-carboxylate (**3h**):* mixture of two diastereoisomers; 89% yield (36 mg), oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 2.9 Hz, 1H), 7.77 (d, J = 2.9 Hz, 1H), 6.90−6.84 (m, 2H), 6.80 (dd, J = 2.6 and 1.1 Hz, 1H), 6.77 (dd, J = 2.6 and 1.2 Hz, 1H), 4.97 (dd, J = 14.5 and 9.1 Hz, 1H), 4.84 (dd, J = 14.8 and 8.1 Hz, 1H), 4.64 (dd, J = 14.8 and 5.8 Hz, 1H), 4.35 (dd, J = 14.5 and 4.6 Hz, 1H), 4.25−4.01 (m, 7H), 3.96 (d, J = 2.8 Hz, 1H), 3.81 (s, 3H), 3.80 (s, 3H), 1.64 (s, 18H), 1.22−1.13 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.7, 13.8, 28.1, 43.7, 43.9, 45.3, 45.7, 55.6, 55.7, 62.2, 62.3, 72.1, 72.5, 84.66, 84.74, 110.0, 110.2, 113.8, 113.9, 116.3, 116.4, 124.5, 125.0, 133.6, 133.8, 148.8, 156.97, 157.01, 168.7, 169.1, 172.6, 173.4; HPLC-MS (ESI) t_r = 9.9 min, 10.2 min; $[M + Na]^+$ = 431.3 m/z, $[2M + Na]^+$ = 839.6 m/z. Anal. Calcd for $C_{19}H_{24}N_2O_8$ (408.15): C, 55.88; H, 5.92; N, 6.86. Found: C, 55.77; H, 5.93; N, 6.87.

3-((R)-1-Ethoxy-3-nitro-1-oxopropan-2-yl)-5-methoxy-2-oxoindoline: mixture of two diastereoisomers, gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.45 (bs, 2H), 6.90−6.73 (m, 6H), 4.96 (dd, J = 14.5 and 9.3 Hz, 1H), 4.76 (dd, J = 14.8 and 8.9 Hz, 1H), 4.49−4.35 (m, 2H), 4.29−4.15 (m, 4H), 4.10 (ddd, J = 8.6, 4.8, and 3.3 Hz, 1H), 4.04−3.92 (m, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 1.25 (t, J = 7.1 Hz, 3H), 1.20 (t, J = 7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.8, 13.9, 43.0, 43.3, 45.5, 45.6, 55.78, 55.84, 62.1, 62.2, 72.0, 72.1, 110.8, 111.6, 111.7, 113.7, 113.8, 126.1, 126.4, 134.6, 134.8, 156.09, 156.14, 169.1, 169.8, 176.5, 176.8; HPLC-MS (ESI) t_r = 5.9 min, 6.2 min; $[M + H]^+$ = 309.2 m/z, $[M + Na]^+$= 331.2, $[2M + Na]^+$ = 639.3 m/z. Anal. Calcd for $C_{14}H_{16}N_2O_6$ (308.10): C, 54.54; H, 5.23; N, 9.09. Found: C, 54.42; H, 5.24; N, 9.12. CSP-HPLC: OD-H 85:15 *n*-Hex/IPA for 15 min, then up to 80/20 in 10 min, 80/20 for 10 min, then up to 70/30 in 10 min, 70/30 up to 41 min; flow rate 0.5 mL/min at room temperature; λ 214 nm; t_r(isomer A) = 24.9 min (major), 33.4 min (minor); t_r(isomer B) = 31.3 min (minor), 36.3 min (major).

*tert-Butyl 3-((R)-1-(benzyloxy)-3-nitro-1-oxopropan-2-yl)-2-oxoindoline-1-carboxylate (**3i**):* mixture of two diastereoisomers; 72% yield (32 mg), oil; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.80 (d, J = 8.2 Hz, 2H), 7.41−6.95 (m, 16H), 5.15 (s, 2H), 5.10 (s, 2H), 5.02 (dd, J = 14.4 and 9.3 Hz, 1H), 4.81 (dd, J = 14.8 and 8.3 Hz, 1H), 4.58 (dd, J = 14.9 and 5.5 Hz, 1H), 4.39 (dd, J = 14.5 and 4.6 Hz, 1H), 4.27−3.93 (m, 4H), 1.64 (s, 9H), 1.63 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.0, 43.6, 43.7, 45.0, 45.4, 67.97, 68.02, 72.2, 84.9, 115.4, 115.5, 123.1, 123.3, 123.5, 124.6, 124.7, 128.4, 128.5, 128.6, 128.7, 129.2, 129.4, 134.4, 134.5, 140.2, 140.5, 148.6, 168.7, 169.1, 172.5, 173.2; HPLC-MS (ESI) t_r = 11.0 min, 11.2 min; $[M + Na]^+$ = 463.3 m/z, $[2M + Na]^+$ = 903.5 m/z. Anal. Calcd for $C_{23}H_{24}N_2O_7$ (440.16): C, 62.72; H, 5.49; N, 6.36. Found: C, 62.71; H, 5.48; N, 6.35.

3-((R)-1-(Benzyloxy)-3-nitro-1-oxopropan-2-yl)-2-oxoindoline: mixture of two diastereoisomers, gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.42 (bs, 2H), 7.39−7.30 (m, 6H), 7.30−7.20 (m, 7H), 7.18 (d, J = 7.5 Hz, 1H), 7.08−6.91 (m, 3H), 6.85 (t, J = 8.4 Hz, 1H), 5.26−5.08 (m, 4H), 5.01 (dd, J = 14.6 and 9.5 Hz, 1H), 4.76 (dd, J = 14.8 and 9.0 Hz, 1H), 4.51−4.38 (m, 2H), 4.16 (m, 1H), 4.10 (m, 1H), 3.98−3.91 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 43.0, 43.3, 44.98, 45.03, 67.8, 67.9, 71.9, 72.3, 110.3, 110.4, 122.96, 122.99, 124.3, 124.4, 124.6, 124.8, 128.4, 128.51, 128.54, 128.6, 128.7, 129.1, 129.3, 134.6, 134.7, 141.2, 141.5, 169.1, 169.7, 176.3, 176.5; HPLC-MS (ESI) t_r = 8.4 min, 8.7 min; $[M + H]^+$ = 341.1 m/z, $[M + Na]^+$ = 363.2 m/z. Anal. Calcd for $C_{18}H_{16}N_2O_5$ (340.11): C, 63.52; H, 4.74; N, 8.23. Found: C, 63.42; H, 4.73; N, 8.22. CSP-HPLC: OJ 90/10 *n*-Hex/IPA for 10 min, then up to 80/20 in 20 min, 80/20 up to 105 min; flow rate 0.5 mL/min at room temperature; λ 214 nm; t_r(isomer A) = 77.1 min (minor), 90.9 min (major); t_r(isomer B) = 84.8 min (major), 100.9 min (minor).

*tert-Butyl 3-((R)-1-(tert-butoxy)-3-nitro-1-oxopropan-2-yl)-2-oxoindoline-1-carboxylate (**3j**):* mixture of two diastereoisomers; 99% yield (40 mg), oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 (d, J = 8.1 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H), 7.40−7.32 (m, 2H), 7.28−7.14 (m, 4H), 5.06 (dd, J = 14.2 and 9.0 Hz, 1H), 4.88 (dd, J = 14.7 and 8.1 Hz, 1H), 4.69 (dd, J = 14.7 and 6.0 Hz, 1H), 4.49 (dd, J = 14.1 and 5.6 Hz, 1H), 4.15 (ddd, J = 8.9 and 5.7 and 2.9 Hz, 1H), 4.00 (ddd, J = 8.1 and 6.0 and 3.3 Hz, 1H), 3.93 (d, J = 3.2 Hz, 1H), 3.82 (d, J = 2.8 Hz, 1H), 1.65 (s, 9H), 1.64 (s, 9H), 1.30 (s, 9H), 1.19 (s, 9H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.3, 27.5, 28.1, 44.5, 44.9, 45.1, 45.5, 72.9, 73.3, 83.5, 84.8, 115.2, 115.3, 123.5, 123.6, 123.7, 124.3, 124.6, 129.0, 129.3, 140.3, 140.7, 148.9, 167.4, 167.9, 172.8, 173.4; HPLC-MS (ESI) t_r = 10.8 min, 11.1 min; $[M + Na]^+$ = 429.4 m/z, $[2M + Na]^+$ = 835.5 m/z. Anal. Calcd

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for $C_{20}H_{26}N_2O_7$ (406.17): C, 59.10; H, 6.45; N, 6.89. Found: C, 58.95; H, 6.44; N, 6.91.

3-((R)-1-(tert-Butoxy)-3-nitro-1-oxopropan-2-yl)-2-oxoindoline: mixture of two diastereoisomers, syrup; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (bs, 2H), 7.32−7.25 (m, 2H), 7.25−7.19 (m, 2H), 7.11−7.03 (m, 2H), 6.95−6.88 (m, 2H), 5.00 (dd, J = 14.2 and 9.3 Hz, 1H), 4.80 (dd, J = 14.7 and 9.1 Hz, 1H), 4.46 (ddd, J = 14.2 and 12.1 and 5.0 Hz, 2H), 4.08−3.96 (m, 2H), 3.91 (d, J = 3.5 Hz, 1H), 3.81 (d, J = 3.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 43.9, 44.0, 45.00, 45.2, 72.3, 73.1, 109.9, 110.0, 122.9, 122.8, 124.4, 124.5, 125.2, 125.4, 129.0, 129.2, 141.1, 141.6, 167.8, 168.7, 176.2, 176.3; HPLC-MS (ESI) t_r = 7.3 min, 7.9 min; $[M + H]^+$ = 251.1 m/z. Anal. Calcd for $C_{11}H_{10}N_2O_5$ (250.06): C, 52.80; H, 4.03; N, 11.20. Found: C, 52.74; H, 4.01; N, 11.23. CSP-HPLC: OJ 90/10 n-Hex/IPA for 10 min, then up to 80/20 in 20 min, 80/20 up to 56 min; flow rate 0.5 mL/min at room temperature; λ 214 nm; t_r(isomer A) = 27.6 min (major), 38.4 min (minor); t_r(isomer B) = 33.0 min (major), 52.2 min (minor).

*tert-Butyl 3-((S)-2-nitro-1-phenylethyl)-2-oxoindoline-1-carboxylate (**3k**):* mixture of two diastereoisomers; 52% yield (20 mg), gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.2 Hz, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.35−7.08 (m, 10H), 7.08−6.95 (m, 5H), 6.63 (d, J = 7.5 Hz, 1H), 5.43−5.29 (m, 2H), 5.12 (dd, J = 13.9 and 7.9 Hz, 1H), 4.92 (dd, J = 13.1 and 9.0 Hz, 1H), 4.25 (td, J = 7.6 and 3.8 Hz, 1H), 4.03 (m, 1H), 3.92 (d, J = 3.7 Hz, 1H), 3.80 (d, J = 7.8 Hz, 1H), 1.65 (s, 18H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.99, 28.01, 45.5, 46.0, 48.2, 48.7, 75.7, 77.1, 84.5, 84.6, 114.9, 115.0, 123.9, 124.1, 124.3, 124.4, 124.6, 124.8, 128.0, 128.2, 128.4, 128.48, 128.53, 128.7, 128.8, 129.0, 134.1, 135.2, 140.2, 140.4, 148.5, 148.6, 173.5, 173.9; HPLC-MS (ESI) t_r = 10.6 min; $[M + Na]^+$ = 405.2 m/z. Anal. Calcd for $C_{21}H_{22}N_2O_5$ (382.15): C, 65.96; H, 5.80; N, 7.33. Found: C, 65.87; H, 5.81; N, 7.32.

3-((S)-2-Nitro-1-phenylethyl)-2-oxoindoline: mixture of two diastereoisomers, amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.00 (m, 14H), 6.93−6.85 (m, 1H), 6.80 (d, J = 7.8 Hz, 1H), 6.67 (d, J = 7.7 Hz, 1H), 6.57 (d, J = 7.6 Hz, 1H), 5.48 (dd, J = 13.1 and 6.7 Hz, 1H), 5.35 (dd, J = 13.7 and 7.3 Hz, 1H), 5.14 (dd, J = 13.7 and 8.0 Hz, 1H), 4.92 (dd, J = 13.1 and 9.1 Hz, 1H), 4.29 (dt, J = 7.7 and 4.0 Hz, 1H), 4.01 (m, 1H), 3.84 (d, J = 3.9 Hz, 1H), 3.73 (d, J = 8.3 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 44.5, 45.3, 47.9, 48.6, 75.8, 77.5, 109.8, 110.0, 122.4, 122.5, 124.4, 125.4, 126.26, 126.32, 128.0, 128.1, 128.40, 128.45, 128.50, 128.53, 128.8, 134.9, 136.0, 141.2, 141.5, 177.4, 177.5; HPLC-MS (ESI) t_r = 7.6 min; $[M + H]^+$ = 283.3 m/z, $[M + Na]^+$ = 305.3 m/z. Anal. Calcd for $C_{16}H_{14}N_2O_3$ (282.10): C, 68.07; H, 5.00; N, 9.92. Found: C, 67.94; H, 5.00; N, 9.96. CSP-HPLC: IC 90/10 n-Hex/IPA for 10 min, then up to 80/20 in 5 min, 80/20 for 15 min, then up to 70/30 in 5 min, 70/30 up to 36 min; flow rate 0.5 mL/min at room temperature; λ 230 nm; t_r(isomer A) = 25.0 min (minor), 26.8 min (major); t_r(isomer B) = 29.7 min (major), 31.7 min (minor).

*tert-Butyl 3-((S)-2-nitro-1-(4-nitrophenyl)ethyl)-2-oxoindoline-1-carboxylate (**3l**):* mixture of two diastereoisomers; 98% yield (42 mg), gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 8.5 Hz, 2H), 8.00 (d, J = 8.8 Hz, 2H), 7.73 (d, J = 8.2 Hz, 1H), 7.57 (d, J = 8.1 Hz, 1H), 7.40−7.30 (m, 2H), 7.30−7.17 (m, 6H), 7.16−7.07 (m, 1H), 6.85 (d, J = 7.6 Hz, 1H), 5.42−5.22 (m, 3H), 4.97 (dd, J = 13.4 and 9.5 Hz, 1H), 4.37 (ddd, J = 8.5 and 6.8 and 3.9 Hz, 1H), 4.32−4.23 (m, 1H), 3.98 (d, J = 3.8 Hz, 1H), 3.88 (d, J = 6.7 Hz, 1H), 1.58 (s, 18H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 27.97, 28.00, 45.1, 45.5, 48.1, 48.5, 75.4, 85.1, 115.2, 115.4, 123.3, 123.6, 123.7, 123.8, 124.4, 124.5, 124.7, 129.2, 129.3, 129.5, 129.6, 140.0, 140.5, 141.5, 142.4, 147.7, 147.9, 148.2, 148.3, 172.8, 173.4; HPLC-MS (ESI) t_r = 10.7 min; $[M + Na]^+$ = 450.2 m/z, $[2M + Na]^+$ = 877.7 m/z. Anal. Calcd for $C_{21}H_{21}N_3O_7$ (427.14): C, 59.01; H, 4.95; N, 9.83. Found: C, 58.85; H, 4.94; N, 9.81.

3-((S)-2-Nitro-1-(4-nitrophenyl)ethyl)-2-oxoindoline: mixture of two diastereoisomers, amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 8.9 Hz, 2H), 8.01 (d, J = 8.8 Hz, 2H), 7.91 (bs, 1H), 7.38−7.23 (m, 6H), 7.19 (t, J = 7.2 Hz, 1H), 7.09 (t, J = 7.6 Hz, 1H), 7.01 (t, J = 7.6 Hz, 1H), 6.87−6.80 (m, 2H), 6.70 (d, J = 7.8 Hz, 1H), 5.41−5.26 (m, 3H), 4.97 (dd, J = 13.3 and 9.4 Hz, 1H), 4.41 (ddd, J = 8.3 and 6.9 and 4.0 Hz, 1H), 4.27 (dt, J = 9.4 and 6.7 Hz, 1H), 3.90 (d, J = 3.9 Hz, 1H), 3.81 (d, J = 6.9 Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 44.3, 44.9, 47.8, 48.3, 75.4, 76.6, 110.2, 110.4, 122.9, 123.0, 123.6, 123.9, 124.3, 125.0, 125.4, 129.1, 129.2, 129.4, 129.5, 140.8, 141.3, 142.1, 142.9, 147.6, 147.9, 176.4, 176.7; HPLC-MS (ESI) t_r = 7.5 min, 7.6 min; $[M + H]^+$ = 328.3 m/z, $[M + Na]^+$ = 350.1 m/z. Anal. Calcd for $C_{16}H_{13}N_3O_5$ (327.09): C, 58.72; H, 4.00; N, 12.84. Found: C, 58.52; H, 4.01; N, 12.85. CSP-HPLC: IC 85:15 n-Hex/IPA for 20 min, then up to 80/20 in 20 min, 80/20 up to 52 min; flow rate 0.5 mL/min at room temperature; λ 214 nm; t_r(isomer A) = 39.0 min (minor), 46.8 min (major); t_r(isomer B) = 43.0 min (major), 45.5 min (minor).

*tert-Butyl 3-((S)-3,3-dimethyl-1-nitrobutan-2-yl)-2-oxoindoline-1-carboxylate (**3m**):* mixture of two diastereoisomers; 62% yield (22 mg), gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.3 Hz, 1H), 7.79 (d, J = 8.2 Hz, 1H), 7.38−7.11 (m, 6H), 4.71−4.47 (m, 4H), 3.82 (s, 1H), 3.74 (s, 1H), 3.05 (ddd, J = 10.4 and 4.7 and 1.7 Hz, 1H), 2.86 (m, 1H), 1.65 (s, 18H), 1.13 (s, 18H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.1, 28.3, 28.6, 33.7, 34.1, 45.3, 45.4, 48.0, 49.7, 73.7, 74.1, 84.4, 84.5, 115.0, 115.6, 123.3, 124.0, 124.4, 124.5, 127.4, 128.4, 128.8, 139.8, 140.8, 149.0, 149.1, 174.0, 175.7; HPLC-MS (ESI) t_r = 10.8 min, 11.2 min; $[M + Na]^+$ = 385.2 m/z, $[2M + Na]^+$ = 747.7 m/z. Anal. Calcd for $C_{19}H_{26}N_2O_5$ (362.18): C, 62.97; H, 7.23; N, 7.73. Found: C, 62.95; H, 7.24; N, 7.74.

3-((S)-3,3-Dimethyl-1-nitrobutan-2-yl)-2-oxoindoline: mixture of two diastereoisomers, amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (bs, 1H), 8.22 (bs, 1H), 7.31−7.16 (m, 4H), 7.13−6.98 (m, 2H), 6.95−6.81 (m, 2H), 4.74−4.47 (m, 4H), 3.72 (s, 1H), 3.66 (s, 1H), 3.06 (ddd, J = 9.9 and 4.9 and 1.7 Hz, 1H), 2.90 (ddd, J = 8.6 and 5.1 and 1.8 Hz, 1H), 1.14 (s, 18H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 28.4, 28.5, 33.7, 34.1, 45.4, 47.1, 48.8, 74.2, 74.6, 109.8, 110.3, 122.3, 122.7, 123.9, 125.1, 126.1, 128.3, 128.6, 129.1, 140.8, 141.8, 177.6, 179.5; HPLC-MS (ESI) t_r = 7.8 min, 8.4 min; $[M + H]^+$ = 263.1 m/z, $[M + Na]^+$ = 285.2 m/z, $[2M + H]^+$ = 525.3 m/z. Anal. Calcd for $C_{14}H_{18}N_2O_3$ (262.13): C, 64.10; H, 6.92; N, 10.68. Found: C, 63.88; H, 6.94; N, 10.70. CSP-HPLC: IC 90/10 n-Hex/IPA for 15 min, then up to 80/20 in 10 min, 80/20 for 10 min, then up to 70/30 in 5 min, 70/30 for 5 min, then up to 1/1 in 1 min, 1/1 up to 53 min; flow rate 0.5 mL/min at room temperature; λ 254 nm; t_r(isomer A) = 31.5 min (major), 39.2 min (minor); t_r(isomer B) = 45.9 min (major), 47.7 min (minor).

*tert-Butyl 3-((R)-1-Ethoxy-2-methyl-3-nitro-1-oxopropan-2-yl)-2-oxoindoline-1-carboxylate (**3n**):* mixture of two diastereoisomers; 57% yield (22 mg), oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92−7.78 (m, 2H), 7.59 (d, J = 7.6 Hz, 1H), 7.41−7.29 (m, 2H), 7.22−7.12 (m, 2H), 7.04 (d, J = 7.6 Hz, 1H), 5.38 (d, J = 13.2 Hz, 1H), 5.15 (d, J = 13.2 Hz, 2H), 4.97 (d, J = 12.4 Hz, 1H), 4.46−4.33 (m, 4H), 3.95 (s, 1H), 3.94 (s, 1H), 1.65 (s, 9H), 1.64 (s, 9H), 1.38 (t, J = 7.2 Hz, 3H), 1.35 (t, J = 6.8 Hz, 3H), 1.13 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) (major isomer) δ 13.9, 14.6, 28.1, 49.1, 49.9, 62.2, 80.0, 85.1, 115.0, 122.6, 124.6, 125.1, 129.4, 140.8, 148.6, 171.6, 172.8; HPLC-MS (ESI) t_r = 10.8 min; $[M + Na]^+$ = 415.4 m/z, $[2M + Na]^+$ = 807.5 m/z. Anal. Calcd for $C_{19}H_{24}N_2O_7$ (392.16): C, 58.16; H, 6.16; N, 7.14. Found: C, 58.08; H, 6.18; N, 7.15.

3-((R)-1-Ethoxy-2-methyl-3-nitro-1-oxopropan-2-yl)-2-oxoindoline: mixture of two diastereoisomers, gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (bs, 1H), 7.57 (bs, 1H), 7.40−7.19 (m, 3H), 7.09−6.94 (m, 3H), 6.88 (d, J = 7.6 Hz, 1H), 6.82 (d, J = 8.2 Hz, 1H), 5.46 (d, J = 13.2 Hz, 1H), 5.17 (d, J = 12.8 Hz, 1H), 5.15 (d, J = 13.2 Hz, 1H), 4.93 (d, J = 12.8 Hz, 1H), 4.48−4.34 (m, 4H), 3.85 (s, 2H), 1.41 (t, J = 7.2 Hz, 3H), 1.37 (t, J = 7.2 Hz, 3H), 1.13 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) (major isomer) δ 14.1, 14.3, 48.4, 49.5, 62.2, 79.8, 109.8, 122.9, 124.3, 125.2, 129.2, 141.4, 171.9, 175.7; HPLC-MS (ESI) t_r = 6.7 min, 7.4 min; $[M + H]^+$ = 293.3 m/z, $[M + Na]^+$ = 315.2 m/z, $[2M + Na]^+$ = 607.4 m/z. Anal. Calcd for $C_{14}H_{16}N_2O_5$ (292.11): C, 57.53; H, 5.52; N, 9.58. Found: C, 57.51; H, 5.54; N, 9.56. CSP-HPLC: IC 90/10 n-Hex/IPA for 10 min, then up to 80/20 in 5 min, 80/20 for 15 min, then up to 70/30 in 15 min, 70/30 up to 47 min; flow rate 0.5 mL/min at room temperature; λ 214 nm; t_r(isomer A) = 23.2 min (major), 29.0 min (minor); t_r(isomer B) = 35.3 min (minor), 41.6 min (major).

*tert-Butyl 3-((2R,3S)-1-ethoxy-3-nitro-1-oxobutan-2-yl)-2-oxoindoline-1-carboxylate (anti-**4b**):* mixture of two diastereoisomers; 71% yield (28 mg), gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (t, J = 8.6 Hz, 2H), 7.39−7.29 (m, 4H), 7.17 (t, J = 7.7 Hz, 2H), 5.67 (dq, J = 9.9 and 6.8 Hz, 1H), 5.30 (dq, J = 9.2 and 6.3 Hz, 1H), 3.99−3.91 (m, 4H), 3.91−3.84 (m, 1H), 3.80 (dd, J = 9.3 and 4.1 Hz, 1H), 3.74 (d, J = 4.3 Hz, 1H), 3.62 (d, J = 4.0 Hz, 1H), 1.78 (d, J = 6.5 Hz, 3H), 1.64

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(m, 21H), 0.99 (t, J = 7.2 Hz, 3H), 0.98 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.5, 13.6, 18.1, 18.9, 28.0, 28.1, 44.1, 45.3, 50.6, 51.5, 61.8, 61.8, 79.5, 81.8, 84.5, 84.7, 115.1, 115.2, 123.4, 123.7, 124.0, 124.4, 124.5, 124.6, 129.1, 129.3, 140.4, 140.5, 148.9, 149.1, 167.9, 168.1, 172.8, 172.9; HPLC-MS (ESI) t_r = 10.3 min, 10.4 min; $[M + Na]^+$ = 415.3 m/z. Anal. Calcd for $C_{19}H_{24}N_2O_7$ (392.16): C, 58.16; H, 6.16; N, 7.14. Found: C, 57.98; H, 6.18; N, 7.14.

3-((2R,3S)-1-Ethoxy-3-nitro-1-oxobutan-2-yl)-2-oxoindoline: mixture of two diastereoisomers, amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (bs, 1H), 8.01 (bs, 1H), 7.34−7.19 (m, 4H), 7.12−7.01 (m, 2H), 6.94−6.83 (m, 2H), 5.62 (dq, J = 9.6 and 6.9 Hz, 1H), 5.36 (dq, J = 8.6 and 6.6 Hz, 1H), 4.08−3.96 (m, 4H), 3.90 (dd, J = 9.6 and 4.4 Hz, 1H), 3.77 (dd, J = 8.5 and 5.2 Hz, 1H), 3.70 (d, J = 4.4 Hz, 1H), 3.60 (d, J = 5.2 Hz, 1H), 1.77 (d, J = 6.6 Hz, 3H), 1.62 (d, J = 6.9 Hz, 3H), 1.02, (t, J = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.67, 13.72, 17.4, 18.7, 44.0, 44.8, 49.8, 50.4, 61.68, 61.73, 79.5, 81.6, 109.8, 109.9, 122.5, 122.8, 124.6, 125.2, 125.3, 125.4, 128.9, 129.0, 141.2, 141.4, 168.3, 168.7, 176.3; HPLC-MS (ESI) t_r = 6.9 min, 7.0 min; $[M + H]^+$ = 293.3 m/z, $[M + Na]^+$ = 315.2 m/z, $[2M + Na]^+$ = 607.4 m/z. Anal. Calcd for $C_{14}H_{16}N_2O_5$ (292.11): C, 57.53; H, 5.52; N, 9.58. Found: C, 57.39; H, 5.51; N, 9.55. CSP-HPLC: IC 90/10 *n*-Hex/IPA for 10 min, then up to 80/20 in 5 min, 80/20 for 20 min, then up to 75/25 in 15 min, 75/25 up to 53 min; flow rate 0.5 mL/min at room temperature; λ 214 nm; t_r(isomer A) = 24.4 min (major), 31.5 min (minor); t_r(isomer B) = 39.8 min (minor), 47.0 min (major).

*tert-Butyl 3-((2R,3S)-1-ethoxy-3-nitro-1-oxopentan-2-yl)-2-oxoindoline-1-carboxylate (anti-**4c**):* mixture of two diastereoisomers; 76% yield (31 mg), gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (t, J = 8.0 Hz, 2H), 7.40−7.22 (m, 4H), 7.20−7.12 (m, 2H), 5.62 (ddd, J = 10.8 and 7.3 and 5.8 Hz, 1H), 5.16 (ddd, J = 10.3 and 8.3 and 5.0 Hz, 1H), 3.92 (q, J = 7.1 Hz, 2H), 3.89−3.81 (m, 3H), 3.77 (dd, J = 10.3 and 3.0 Hz, 1H), 3.62 (d, J = 4.3 Hz, 1H), 3.54−3.47 (m, 1H), 2.19−2.05 (m, 2H), 2.00−1.89 (m, 2H), 1.65 (s, 18H), 1.08 (t, J = 7.3 Hz, 3H), 1.03 (t, J = 7.3 Hz, 3H), 0.95 (t, J = 7.3 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 9.6, 10.5, 13.4, 13.5, 26.3, 26.6, 28.0, 28.1, 44.0, 45.6, 49.9, 50.8, 61.76, 61.78, 84.5, 84.6, 85.4, 88.9, 115.0, 115.1, 123.1, 123.6, 123.9, 124.4, 124.6, 124.7, 129.1, 129.2, 140.4, 140.5, 148.9, 149.1, 167.9, 168.1, 172.6, 172.9; HPLC-MS (ESI) t_r = 10.9 min, 11.0 min; $[M + Na]^+$ = 429.2 m/z. Anal. Calcd for $C_{20}H_{26}N_2O_7$ (406.17): C, 59.10; H, 6.45; N, 6.89. Found: C, 59.04; H, 6.43; N, 6.92.

3-((2R,3S)-1-Ethoxy-3-nitro-1-oxopentan-2-yl)-2-oxoindoline: mixture of two diastereoisomers, gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (bs, 2H), 7.39−7.17 (m, 4H), 7.14−6.98 (m, 2H), 6.95−6.81 (m, 2H), 5.60 (ddd, J = 10.6 and 8.4 and 4.7 Hz, 1H), 5.25−5.12 (m, 1H), 4.00−3.80 (m, 5H), 3.73 (dd, J = 9.9 and 3.7 Hz, 1H), 3.56 (d, J = 4.4 Hz, 1H), 3.45 (d, J = 3.7 Hz, 1H), 2.24−2.05 (m, 2H), 2.05−1.87 (m, 2H), 1.11−1.05 (m, 3H), 1.02 (t, J = 7.3 Hz, 3H), 0.99−0.91 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 9.7, 10.5, 13.5, 13.6, 26.2, 26.3, 44.1, 45.4, 49.3, 49.7, 61.6, 61.7, 85.5, 88.9, 109.9, 110.0, 122.5, 122.7, 124.4, 124.9, 125.3, 125.4, 128.9, 129.0, 141.6, 141.7, 168.2, 168.7, 176.7, 177.0; HPLC-MS (ESI) t_r = 7.8 min, 7.9 min; $[M + H]^+$ = 307.3 m/z, $[M + Na]^+$ = 329.1 m/z, $[2M + Na]^+$ = 635.5 m/z. Anal. Calcd for $C_{15}H_{18}N_2O_5$ (306.12): C, 58.82; H, 5.92; N, 9.15. Found: C, 58.65; H, 5.91; N, 9.17. CSP-HPLC: IC 90/10 *n*-Hex/IPA for 10 min, then up to 80/20 in 5 min, 80/20 for 20 min, then up to 75/25 in 15 min, 75/25 up to 58 min; flow rate 0.5 mL/min at room temperature; λ 230 nm; t_r(isomer A) = 21.9 min (major), 27.9 min (minor); t_r(isomer B) = 32.6 min (minor), 51.0 min (major).

*(2R,3S)-1-Ethyl 6-methyl 2-(1-(tert-butoxycarbonyl)-2-oxoindolin-3-yl)-3-nitrohexanedioate (anti-**4d**):* mixture of two diastereoisomers; 83% yield (39 mg), oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91−7.79 (m, 2H), 7.40−7.28 (m, 4H), 7.22−7.13 (m, 2H), 5.70−5.60 (m, 1H), 5.41−5.26 (m, 1H), 4.06−3.92 (m, 3H), 3.92−3.77 (m, 1H), 3.72 (s, 3H), 3.70 (s, 3H), 3.65 (d, J = 4.0 Hz, 1H), 3.53 (d, J = 2.4 Hz, 1H), 2.60−2.19 (m, 8H), 1.65 (s, 18H), 0.98 (t, J = 7.2 Hz, 3H), 0.93 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 13.5, 27.8, 27.9, 28.0, 28.1, 29.8, 30.3, 44.0, 45.4, 49.9, 50.7, 51.9, 61.9, 62.0, 83.5, 84.5, 84.7, 86.3, 115.1, 115.2, 123.6, 123.7, 124.4, 124.5, 124.6, 124.7, 129.1, 129.3, 140.4, 140.5, 148.9, 149.0, 167.7, 167.8, 171.8, 172.5, 172.8; HPLC-MS (ESI) t_r = 11.2 min; $[M + Na]^+$ = 487.3 m/z. Anal. Calcd for $C_{22}H_{28}N_2O_9$ (464.18): C, 56.86; H, 6.08; N, 6.03. Found: C, 56.69; H, 6.08; N, 6.05.

(2R,3S)-1-Ethyl 6-methyl 3-nitro-2-(2-oxoindolin-3-yl)-hexanedioate: mixture of two diastereoisomers, gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71−7.50 (bs, 2H), 7.34−7.20 (m, 4H), 7.05 (t, J = 8.0 Hz, 2H), 6.90−6.81 (m, 2H), 5.68−5.59 (m, 1H), 5.41−5.29 (m, 1H), 4.05−3.92 (m, 4H), 3.86 (dd, J = 10.0 and 4.4 Hz, 1H), 3.74 (dd, J = 9.2 and 4.4 Hz, 1H), 3.72 (s, 3H), 3.69 (s, 3H), 3.59 (d, J = 4.4 Hz, 1H), 3.51 (d, J = 4.4 Hz, 1H), 2.54−2.39 (m, 6H), 2.28−2.20 (m, 2H), 1.03−0.94 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 13.7, 27.4, 27.7, 29.9, 30.4, 43.9, 44.9, 49.4, 49.7, 51.9, 61.8, 61.9, 83.5, 86.1, 109.6, 109.7, 122.6, 122.9, 124.5, 124.9, 125.2, 125.3, 129.0, 129.1, 141.2, 141.4, 168.0, 168.4, 171.9, 171.9, 175.7, 175.9; HPLC-MS (ESI) t_r = 7.3 min; $[M + H]^+$ = 365.3 m/z, $[M + Na]^+$ = 387.2 m/z, $[2M + Na]^+$ = 751.5 m/z. Anal. Calcd for $C_{17}H_{20}N_2O_7$ (364.13): C, 56.04; H, 5.53; N, 7.69. Found: C, 55.83; H, 5.53; N, 7.68. CSP-HPLC: IC 80/20 *n*-Hex/IPA for 10 min, then up to 75/25 in 5 min, 75/25 for 25 min, then up to 65/35 in 15 min, 65/35 up to 67 min; flow rate 0.5 mL/min at room temperature; λ 254 nm; t_r(isomer A) = 26.8 min (major), 33.3 min (minor); t_r(isomer B) = 34.5 min (minor), 63.1 min (major).

*tert-Butyl 3-((2R,3S)-1-ethoxy-3-nitro-1-oxo-4-phenylbutan-2-yl)-2-oxoindoline-1-carboxylate (anti-**4e**):* mixture of two diastereoisomers; 72% yield (34 mg), amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88−7.78 (m, 2H), 7.39−7.24 (m, 12H), 7.22−7.13 (m, 4H), 5.86 (ddd, J = 4.4 and 8.4 and 10.4 Hz, 1H), 5.46 (dt, J = 2.8 and 10.4 Hz, 1H), 3.98−3.84 (m, 6H), 3.67 (d, J = 4.0 Hz, 1H), 3.53 (d, J = 2.8 Hz, 1H), 3.45 (dd, J = 2.8 and 14.4 Hz, 1H), 3.32 (dd, J = 10.8 and 14.4 Hz, 1H), 3.28−3.16 (m, 2H), 1.66 (s, 9H), 1.65 (s, 9H), 0.97 (t, J = 7.2 Hz, 3H), 0.95 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 13.5, 28.0, 28.1, 39.0, 39.1, 44.2, 45.6, 49.8, 50.7, 61.9, 62.0, 84.6, 84.7, 85.7, 89.2, 115.1, 115.2, 123.0, 123.7, 123.8, 124.4, 124.6, 124.7, 127.7, 127.8, 128.8, 128.8, 128.9, 128.9, 129.0, 129.1, 129.3, 134.1, 135.1, 140.4, 140.5, 148.9, 168.0, 168.0, 172.4, 172.9; HPLC-MS (ESI) t_r = 12.1 min, 12.4 min; $[M + Na]^+$ = 491.3 m/z, $[2M + Na]^+$ = 959.6 m/z. Anal. Calcd for $C_{25}H_{28}N_2O_7$ (468.19): C, 64.09; H, 6.02; N, 5.98. Found: C, 64.02; H, 6.00; N, 6.00.

3-((2R,3S)-1-Ethoxy-3-nitro-1-oxo-4-phenylbutan-2-yl)-2-oxoindoline: mixture of two diastereoisomers, amorphous solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12−7.89 (bs, 2H), 7.40−7.21 (m, 13H), 7.17 (d, J = 7.6 Hz, 1H), 7.13−7.00 (m, 2H), 6.96−6.82 (m, 2H), 5.88−5.79 (m, 1H), 5.53 (dt, J = 2.8 and 10.0 Hz, 1H), 4.08−3.92 (m, 4H), 3.90 (dd, J = 2.0 and 9.6 Hz, 1H), 3.82 (dd, J = 4.0 and 9.2 Hz, 1H), 3.63 (d, J = 4.0 Hz, 1H), 3.52 (d, J = 4.0 Hz, 1H), 3.43 (dd, J = 3.6 and 14.8 Hz, 1H), 3.35 (dd, J = 10.0 and 14.4 Hz, 1H), 3.27−3.10 (m, 2H), 1.06 (t, J = 7.6 Hz, 3H), 0.99 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 13.7, 38.5, 39.0, 44.3, 45.3, 49.3, 49.7, 61.8, 61.9, 85.8, 89.1, 110.0, 110.2, 122.6, 122.9, 124.5, 124.7, 124.8, 125.3, 127.6, 127.7, 128.8, 128.8, 128.9, 128.9, 129.0, 129.1, 134.4, 135.3, 141.4, 141.6, 168.3, 168.6, 176.3, 176.6; HPLC-MS (ESI) t_r = 9.1 min, 9.2 min; $[M + H]^+$ = 369.4 m/z, $[M + Na]^+$ = 391.2 m/z, $[2M + Na]^+$ = 759.5 m/z. Anal. Calcd for $C_{20}H_{20}N_2O_5$ (368.14): C, 65.21; H, 5.47; N, 7.60. Found: C, 65.15; H, 5.48; N, 7.59. CSP-HPLC: IC 90/10 *n*-Hex/IPA for 15 min, then up to 80/20 in 10 min, 80/20 for 15 min, then up to 70/30 in 10 min, 70/30 for 5 min, then up to 1/1 in 5 min, 1/1 up to 76 min; flow rate 0.5 mL/min at room temperature; λ 214 nm; t_r(isomer A) = 27.2 min (major), 45.7 min (minor); t_r(isomer B) = 39.8 min (minor), 70.0 min (major).

*tert-Butyl 3-((2R,3S)-1-ethoxy-2-methyl-3-nitro-1-oxobutan-2-yl)-2-oxoindoline-1-carboxylate (**5**):* major diastereoisomer; 72% yield (29 mg), syrup; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.0 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 7.13 (t, J = 8.0 Hz, 1H), 7.0 (d, J = 6.8 Hz, 1H), 5.50 (q, J = 6.8 Hz, 1H), 4.41−4.30 (m, 2H), 4.23 (s, 1H), 1.96 (d, J = 7.2 Hz, 3H), 1.65 (s, 9H), 1.36 (t, J = 6.8 Hz, 3H), 1.05 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 15.8, 15.8, 28.1, 48.9, 51.4, 62.2, 85.1, 88.5, 115.0, 124.1, 124.7, 129.2, 129.7, 140.7, 148.7, 170.6, 172.7; HPLC-MS (ESI) t_r = 11.6 min; $[M + Na]^+$ = 429.4 m/z; $[\alpha]_D^{25}$ = 19° (c = 0.48, CH_2Cl_2). Anal. Calcd for $C_{20}H_{26}N_2O_7$ (406.17): C, 59.10; H, 6.45; N, 6.89. Found: C, 59.04; H, 6.45; N, 6.91.

3-((2R,3S)-1-Ethoxy-2-methyl-3-nitro-1-oxobutan-2-yl)-2-oxoindoline: major diastereoisomer, syrup; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68 (bs, 1H), 7.05−6.97 (m, 2H), 6.90−6.84 (m, 2H), 5.59 (q, J = 6.4 Hz,

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1H), 4.40−4.31 (m, 2H), 4.12 (s, 1H), 1.95 (d, J = 6.4 Hz, 3H), 1.37 (t, J = 7.2 Hz, 3H), 1.08 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 15.7, 15.8, 48.6, 50.7, 62.0, 88.2, 109.7, 123.0, 124.8, 129.0, 129.1, 141.3, 175.6, 178.5; HPLC-MS (ESI) t_r = 8.2 min; $[M + H]^+$ = 307.3 m/z, $[M + Na]^+$ = 329.1 m/z; $[\alpha]_D^{25}$ = 13° (c = 0.13, CH_2Cl_2). Anal. Calcd for $C_{15}H_{18}N_2O_5$ (306.12): C, 58.82; H, 5.92; N, 9.15. Found: C, 58.58; H, 5.92; N, 9.16. CSP-HPLC: IC 90/10 n-Hex/IPA for 10 min, then up to 80/20 in 5 min, 80/20 up to 25 min; flow rate 0.5 mL/min at room temperature; λ 214 nm; t_r(major isomer) = 14.5 min (major), 17.8 min (minor).

Synthesis of (*S*)-*tert*-Butyl 3-((*R*)-2,5-Dioxo-1-phenylpyrrolidin-3-yl)-3-((2*R*,3*S*)-1-ethoxy-3-nitro-1-oxobutan-2-yl)-2-oxoindoline-1-carboxylate (6). (*E*)-*tert*-Butyl 3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate (**2c**; 0.1 mmol, 31.7 mg) was added to a solution of **VI** (10 mol %) in DCM (0.15 mL), and then nitroethane **1b** (0.5 mmol) was added at 0 °C. The mixture was stirred at the same temperature until complete conversion (about 4.5 h). The solvent and the excess of **1b** were quickly removed under vacuum (without heating), DCM (0.3 mL) was added, and *N*-phenylmaleimide (0.2 mmol) was finally added at 0 °C. The conversion was monitored by TLC and ^{1}H NMR until full conversion (1.5 h). The crude reaction mixture was directly purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 9/1): 81% yield (46 mg), gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, J = 8.4 Hz, 1H), 7.48−7.37 (m, 4H), 7.27−7.25 (m, 1H), 7.20−7.13 (m, 3H), 5.95−5.85 (m, 1H), 4.89 (d, J = 4.8 Hz, 1H), 3.87−3.81 (m, 3H), 2.92 (dd, J = 9.2 and 18.0 Hz, 1H), 2.11 (dd, J = 5.2 and 18.0 Hz, 1H), 1.69 (s, 9H), 1.64 (d, J = 7.2 Hz, 3H), 0.94 (t, J = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 18.6, 28.1, 30.7, 42.0, 52.0, 52.8, 61.6, 79.0, 85.4, 115.7, 123.8, 124.4, 125.1, 126.4, 129.0, 129.2, 130.7, 131.1, 140.7, 144.6, 148.4, 168.2, 173.1, 174.4, 174.7; HPLC-MS (ESI) t_r = 10.9 min; $[M - Boc + H]^+$ = 466.4 m/z, $[M + H_2O]^+$ = 583.4 m/z; $[\alpha]_D^{25}$ = 107° (c = 0.71, CH_2Cl_2). Anal. Calcd for $C_{29}H_{31}N_3O_9$ (565.21): C, 61.59; H, 5.52; N, 7.43. Found: C, 61.49; H, 5.54; N, 7.40. The absolute configuration of the stereocenters generated in the addition of *N*-phenylmaleimide was not experimentally determined, but it was indicated on the basis of that obtained with the same catalyst promoting the same reaction on similar substrates.[20]

Synthesis of (*R*)-*tert*-Butyl 3-(2,2-Bis(phenylsulfonyl)ethyl)-3-((2*R*,3*S*)-1-ethoxy-3-nitro-1-oxobutan-2-yl)-2-oxoindoline-1-carboxylate (7). (*E*)-*tert*-Butyl 3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate (**2c**; 0.1 mmol, 31.7 mg) was added to a solution of **VI** (10 mol %) in DCM (0.15 mL), and then nitroethane **1b** (0.5 mmol) was added at 0 °C. The mixture was stirred at the same temperature until complete conversion (about 4.5 h). The solvent and the excess of **1b** were quickly removed under vacuum (without heating), toluene (0.6 mL) was added, and 1,1-bis(benzenesulfonyl)-ethylene (0.2 mmol) was finally added at −10 °C. The conversion was monitored by TLC and ^{1}H NMR until full conversion (overnight). The reaction mixture was quenched with 2 mL of HCl (1 N) at 0 °C and extracted with ethyl acetate (3 × 3 mL). The organic phases were collected and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the product was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 8/2): 68% yield (48 mg), syrup; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99−7.93 (m, 3H), 7.79 (d, J = 7.2 Hz, 2H), 7.73−7.66 (m, 2H), 7.61−7.50 (m, 5H), 7.44 (t, J = 7.6 Hz, 1H), 7.27−7.24 (m, 1H), 5.16−5.09 (m, 1H), 4.41 (dd, J = 3.2 and 6.0 Hz, 1H), 4.13 (d, J = 5.2 Hz, 1H), 4.01 (q, J = 7.2 Hz, 2H), 2.94 (dd, J = 5.6 and 16.0 Hz, 1H), 2.85 (dd, J = 2.8 and 16.0 Hz, 1H), 1.64 (s, 9H), 1.38 (d, J = 6.8 Hz, 3H), 1.07 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 17.4, 28.1, 29.6, 50.9, 55.9, 61.8, 79.2, 79.4, 84.8, 116.0, 124.7, 125.6, 126.2, 128.9, 129.0, 129.7, 130.1, 131.0, 134.5, 134.9, 135.6, 137.7, 140.7, 148.8, 168.0, 174.3; HPLC-MS (ESI) t_r = 11.9 min; $[M\text{-}Boc+H]^+$ = 601.3 m/z, $[M + H_2O]^+$ = 718.4 m/z; $[\alpha]_D^{25}$ = 8° (c = 0.54, CH_2Cl_2). Anal. Calcd for $C_{33}H_{36}N_2O_{11}S_2$ (700.18): C, 56.56; H, 5.18; N, 4.00. Found: C, 56.38; H, 5.17; N, 4.01. The absolute configuration of the stereocenter generated in the addition of 1,1-bis(benzenesulfonyl)ethylene was not experimentally determined, but it was indicated on the basis of that obtained with the same catalyst promoting the same reaction on similar substrates.[21b]

Synthesis of (*R*)-*tert*-Butyl 3-((2*R*,3*S*)-1-Ethoxy-3-nitro-1-oxobutan-2-yl)-3-((*S*)-2-nitro-1-phenylethyl)-2-oxoindoline-1-carboxylate (8). (*E*)-*tert*-Butyl 3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate (**2c**; 0.1 mmol, 31.7 mg) was added to a solution of **VI** (10 mol %) in DCM (0.15 mL), and then nitroethane **1b** (0.5 mmol) was added at 0 °C. The mixture was stirred at the same temperature until complete conversion (about 4.5 h). The solvent and the excess of **1b** were quickly removed under vacuum (without heating), DCM (0.3 mL) was added, and *trans*-β-nitrostyrene (0.2 mmol) was finally added at −40 °C. The conversion was monitored by TLC and ^{1}H NMR (90% of conversion after 24 h). The reaction mixture was quenched with 2 mL of HCl (1 N) and extracted with ethyl acetate (3 × 2 mL). The organic phases were collected and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the product was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 9/1): 76% yield (41 mg), syrup. Major diastereoisomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88−7.82 (m, 1H), 7.65−7.41 (m, 3H), 7.23−7.15 (m, 2H), 7.10−6.97 (m, 2H), 6.86 (d, J = 7.6 Hz, 1H), 5.37−5.23 (m, 2H), 4.52−4.36 (m, 3H), 4.17 (dd, J = 3.2 and 10.4 Hz, 1H), 4.13 (d, J = 6.8 Hz, 1H), 1.64 (d, J = 7.2 Hz, 3H), 1.63 (s, 9H), 1.39 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 17.8, 28.0, 50.0, 51.9, 55.8, 62.9, 75.1, 81.6, 85.1, 114.8, 115.2, 123.7, 124.4, 124.6, 126.3, 127.9, 128.4, 129.1, 129.8, 132.8, 139.8, 147.8, 168.9, 174.2; HPLC-MS (ESI) t_r = 12.1 min; $[M + Na]^+$ = 564.3 m/z, $[2M + Na]^+$ = 1105.7 m/z; $[\alpha]_D^{25}$ = 16° (c = 0.91, CH_2Cl_2). Anal. Calcd for $C_{27}H_{31}N_3O_9$ (541.21): C, 59.88; H, 5.77; N, 7.76. Found: C, 59.65; H, 5.77; N, 7.77. The absolute configuration of the stereocenters generated in the addition of *trans*-β-nitrostyrene was not experimentally determined, but it was indicated on the basis of that obtained with the same catalyst promoting the same reaction on similar substrates.[22b]

Synthesis of (*S*)-*tert*-Butyl 3-((2*R*,3*S*)-1-Ethoxy-3-nitro-1-oxobutan-2-yl)-2-oxo-3-((*R*)-3-oxocyclohexyl)indoline-1-carboxylate (9). (*E*)-*tert*-Butyl 3-(2-ethoxy-2-oxoethylidene)-2-oxoindoline-1-carboxylate (**2c**; 0.1 mmol, 31.7 mg) was added to a solution of **VI** (10 mol %) in DCM (0.15 mL), and then nitroethane **1b** (0.5 mmol) was added at 0 °C. The mixture was stirred at the same temperature until complete conversion (about 4.5 h). The reaction mixture was quenched with 2 mL of HCl (1 N) at 0 °C and extracted with DCM (3 × 2 mL). The organic phases were collected and dried over Na_2SO_4. The solvent was evaporated under reduced pressure (without heating), and the crude mixture was directly used in the next transformation. Catalyst **X**·3HCl (10 mol %), triethylamine (30 mol %), and benzoic acid (20 mol %) were dissolved in toluene (0.3 mL). After the mixture was stirred at room temperature for 10 min, 2-cyclohexen-1-one (0.12 mmol) was added followed by the addition of crude **4b** dissolved in toluene (0.3 mL). The mixture was stirred at room temperature for 48 h. The crude reaction mixture was directly purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 85/15): 65% yield (32 mg), gum; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.4 Hz, 1H), 7.41 (d, J = 7.6 Hz, 1H), 7.37 (t, J = 6.4 Hz, 1H), 7.20 (t, J = 6.8 Hz, 1H), 5.46−5.39 (m, 1H), 4.16 (d, J = 5.2 Hz, 1H), 3.95−3.87 (m, 2H), 2.45−2.33 (m, 3H), 2.10−2.03 (m, 2H), 1.90−1.78 (m, 2H), 1.66 (s, 9H), 1.58−1.46 (m, 2H), 1.49 (d, J = 6.8 Hz, 3H), 1.03 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 18.2, 24.0, 25.6, 28.1, 40.7, 42.3, 43.1, 52.7, 54.8, 61.7, 79.4, 85.0, 115.1, 124.4, 124.8, 126.1, 129.6, 140.7, 148.6, 168.2, 175.1, 208.7; HPLC-MS (ESI) t_r = 10.7 min; $[M - Boc + H]^+$ = 389.3 m/z, $[M + H_2O]^+$ = 506.5 m/z, $[2M + Na]^+$ = 999.8 m/z; $[\alpha]_D^{25}$ = −13° (c = 1.02, CH_2Cl_2). Anal. Calcd for $C_{25}H_{32}N_2O_8$ (488.22): C, 61.46; H, 6.60; N, 5.73. Found: C, 61.35; H, 6.59; N, 5.75. The absolute configuration of the stereocenters generated in the addition of 2-cyclohexen-1-one was not experimentally determined, but it was indicated on the basis of that obtained with the same catalyst promoting the same reaction on similar substrates.[10p]

Synthesis of (*S*)-*tert*-Butyl 3-((2*R*,3*S*)-1-Ethoxy-3-nitro-1-oxobutan-2-yl)-2-oxo-3-((*R*)-4-oxobutan-2-yl)indoline-1-carboxylate (10). To a solution of catalyst **XI** (20 mol %) and crude product **4b** (0.1 mmol, prepared as described for product **9**) in DCM (1 mL) at −40 °C were added benzoic acid (20 mol %) and then crotonaldehyde (0.15 mmol). After it was stirred at the same temperature for 24 h, the reaction mixture was quenched with 2 mL of HCl (1 N) at 0 °C and

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extracted with DCM (3 × 2 mL). The organic phases were collected and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the crude mixture was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 9/1): 71% yield (33 mg), gum; mixture of two diastereoisomers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.62 (d, J = 2.0 Hz, 1H), 9.61 (d, J = 2.4 Hz, 1H), 7.85 (d, J = 8.4 Hz, 2H), 7.43−7.32 (m, 4H), 7.20 (t, J = 7.6 Hz, 2H), 5.50−5.43 (m, 1H), 5.30−5.23 (m, 1H), 4.13 (d, J = 5.6 Hz, 1H), 4.12 (d, J = 5.6 Hz, 1H), 3.99−3.88 (m, 4H), 2.86−2.77 (m, 2H), 2.65 (d, J = 16.4 Hz, 1H), 2.53 (d, J = 17.6 Hz, 1H), 2.23 (ddd, J = 2.8, 10.8, and 14.0 Hz, 1H), 2.08 (ddd, J = 2.4 and 10.4 and 12.4 Hz, 1H), 1.66 (s, 18H), 1.53 (d, J = 6.8 Hz, 3H), 1.51 (d, J = 6.8 Hz, 3H), 1.06 (t, J = 7.2 Hz, 3H), 1.02 (t, J = 7.2 Hz, 3H), 0.96 (d, J = 6.8 Hz, 3H), 0.78 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.6, 13.7, 15.0, 18.1, 28.1, 32.6, 33.2, 45.4, 45.7, 53.0, 53.0, 54.7, 61.7, 61.8, 79.3, 79.9, 84.8, 84.9, 115.0, 115.1, 124.3, 124.4, 124.5, 124.7, 126.3, 126.3, 129.5, 140.3, 140.6, 148.6, 148.7, 168.1, 168.3, 175.5, 175.7, 199.5, 200.0; HPLC-MS (ESI) t_r = 10.7 min; $[M - Boc + H]^+$ = 363.4 m/z, $[M + H_2O]^+$ = 480.4 m/z, $[M + Na]^+$ = 485.3 m/z, $[2M + Na]^+$ = 947.8 m/z. Anal. Calcd for $C_{23}H_{30}N_2O_8$ (462.20): C, 59.73; H, 6.54; N, 6.06. Found: C, 59.68; H, 6.52; N, 6.08. The absolute configuration of the stereocenters generated in the addition of crotonaldehyde was not experimentally determined, but it was indicated on the basis of that obtained with the same catalyst promoting the same reaction on similar substrates.[8c]

Synthesis of *tert*-Butyl 3-((2*R*,3*S*)-3-Amino-1-ethoxy-1-oxobutan-2-yl)-2-oxoindoline-1-carboxylate (11a,b). Compound **4b** (0.38 mmol, 149 mg) was dissolved in EtOH (5.5 mL), Raney nickel (6 drops of the commercially available suspension in water) was added, and the reaction mixture was stirred at room temperature under an H_2 balloon overnight. Then it was filtered and washed with ethyl acetate and DCM. The solvent was removed under reduced pressure, and the diastereomeric mixture of **11a** and **11b** (dr = 54/46) was obtained pure: 95% yield (131 mg), oil; mixture of two diastereoisomers; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (bs, 2H), 7.31−7.22 (m, 4H), 7.18 (d, J = 6.8 Hz, 1H), 7.14−7.09 (m, 2H), 7.04 (t, J = 7.2 Hz, 1H), 6.43 (bs, 2H), 4.29 (d, J = 10.8 Hz, 2H), 4.24−4.16 (m, 2H), 3.98−3.84 (m, 2H), 3.28 (dd, J = 8.8 and 10.0 Hz, 1H), 3.09 (dd, J = 8.8 and 10.0 Hz, 1H), 1.53 (s, 9H), 1.52 (s, 9H), 1.44 (d, J = 6.0 Hz, 3H), 1.39 (d, J = 6.0 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H), 0.96 (t, J = 7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.6, 14.1, 21.3, 21.6, 28.4, 45.2, 47.4, 50.4, 51.0, 52.6, 54.4, 61.3, 61.8, 80.1, 80.3, 124.5, 124.7, 125.0, 126.7, 127.7, 128.1, 128.2, 137.1, 137.2, 151.0, 153.8, 169.5, 170.0, 171.8, 175.2; HPLC-MS (ESI) t_r = 7.4 min, 8.0 min; $[M - Boc + H]^+$ = 263.3 m/z, $[M + H]^+$ = 363.4 m/z, $[2M + Na]^+$ = 747.7 m/z. Anal. Calcd for $C_{19}H_{26}N_2O_5$ (362.18): C, 62.97; H, 7.23; N, 7.73. Found: C, 62.84; H, 7.22; N, 7.72.

Procedure for the Stereoconvergent Epimerization to (*R*)-*tert*-Butyl 3-((2*R*,3*S*)-3-Amino-1-ethoxy-1-oxobutan-2-yl)-2-oxoindoline-1-carboxylate (11a). The diastereomeric mixture of **11a** and **11b** (dr = 54/46; 0.1 mmol, 36.2 mg) was dissolved in acetone (0.6 mL), and K_2CO_3 (0.2 mmol) was added. The reaction mixture was stirred at 50 °C for 24 h, and the conversion was monitored by ^{1}H NMR. After completion, the solvent was removed, the residue was dissolved in water (3 mL), and this solution was extracted with DCM (3 × 3 mL). The organic phases were collected and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and compound **11a** was obtained pure: 95% yield, 34 mg, oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (bs, 1H), 7.31−7.27 (m, 2H), 7.18 (d, J = 6.8 Hz, 1H), 7.12 (t, J = 7.2 Hz, 1H), 6.22 (bs, 1H), 4.28 (d, J = 10.4 Hz, 1H), 4.24−4.16 (m, 2H), 3.97−3.90 (m, 1H), 3.09 (dd, J = 10.8 and 8.0 Hz, 1H), 1.52 (s, 9H), 1.44 (d, J = 6.0 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 21.6, 28.4, 47.4, 51.0, 54.3, 61.8, 80.1, 124.6, 125.0, 127.6, 128.2, 128.4, 137.2, 153.7, 171.8, 175.2; HPLC-MS (ESI) t_r = 8.0 min; $[M - Boc + H]^+$ = 263.1 m/z, $[M + H]^+$ = 363.2 m/z, $[2M + Na]^+$ = 747.2 m/z; $[\alpha]_D^{25}$ = 34° (c = 0.99, CH_2Cl_2). Anal. Calcd for $C_{19}H_{26}N_2O_5$ (362.18): C, 62.97; H, 7.23; N, 7.73. Found: C, 62.77; H, 7.24; N, 7.76.

Synthesis of 12a,b. Compound **4b** (0.2 mmol, 78.5 mg) was dissolved in MeOH (3.5 mL), and Pd on C (20% w/w) was added. The reaction mixture was stirred at room temperature under an H_2 balloon overnight. Then it was filtered and washed with ethyl acetate and DCM. The solvent was evaporated under reduced pressure, and the crude mixture was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 1/1): 90% yield, 68 mg, oil.

*(R)-tert-Butyl 3-((2R,3S)-1-ethoxy-3-(hydroxyamino)-1-oxobutan-2-yl)-2-oxoindoline-1-carboxylate (**12a**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (bs, 1H), 7.28−7.23 (m, 1H), 7.15−7.06 (m, 1H), 7.02−6.97 (m, 2H), 4.44−4.37 (m, 1H), 4.27 (d, J = 9.6 Hz, 1H), 3.94−3.76 (m, 2H), 3.20 (dd, J = 10.0 and 8.4 Hz, 1H), 1.54 (s, 9H), 1.44 (d, J = 5.6 Hz, 3H), 0.92 (t, J = 7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.5, 18.3, 28.4, 42.2, 48.8, 55.7, 61.5, 80.5, 118.9, 125.0, 127.3, 128.5, 129.7, 136.9, 153.4, 168.3, 169.4; HPLC-MS (ESI) t_r = 7.0 min; $[M - Boc + H]^+$ = 279.4 m/z, $[2M + Na]^+$ = 779.6 m/z; $[\alpha]_D^{25}$ = −5° (c = 0.67, CH_2Cl_2). Anal. Calcd for $C_{19}H_{26}N_2O_6$ (378.18): C, 60.30; H, 6.93; N, 7.40. Found: C, 60.28; H, 6.91; N, 7.39.

*(S)-tert-Butyl 3-((2R,3S)-1-ethoxy-3-(hydroxyamino)-1-oxobutan-2-yl)-2-oxoindoline-1-carboxylate (**12b**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (bs, 1H), 7.32−7.27 (m, 1H), 7.18−6.99 (m, 3H), 4.31−4.18 (m, 3H), 3.97−3.91 (m, 1H), 2.87 (t, J = 8.4 Hz, 1H), 1.53 (s, 9H), 1.47 (d, J = 5.6 Hz, 3H), 1.27 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 19.0, 28.4, 50.5, 51.3, 56.6, 62.1, 80.3, 118.6, 124.6, 128.2, 128.4, 129.7, 137.2, 153.7, 169.3, 171.4; HPLC-MS (ESI) t_r = 7.6 min; $[M - Boc + H]^+$ = 279.2 m/z, $[2M + Na]^+$ = 779.6 m/z; $[\alpha]_D^{25}$ = 8° (c = 0.93, CH_2Cl_2). Anal. Calcd for $C_{19}H_{26}N_2O_6$ (378.18): C, 60.30; H, 6.93; N, 7.40. Found: C, 60.10; H, 6.94; N, 7.39.

Procedure for the Stereoconvergent Epimerization to 12a. A diastereomeric mixture of **12a** and **12b** (dr = 60/40; 0.1 mmol, 37.8 mg) was dissolved in EtOH (0.7 mL), and $NaHCO_3$ (10 drops of a saturated solution) was added. The reaction mixture was stirred at room temperature for 48 h, and the conversion was monitored by ^{1}H NMR. After completion, water (3 mL) was added to the mixture, and it was extracted with ethyl acetate (3 × 3 mL). The organic phases were collected and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and compound **12a** was obtained pure (90% yield, 34 mg, oil).

Synthesis of ((2*S*,3*R*,3a*R*)-2,8-Dimethyl-2,3,3a,8-tetrahydropyrrolo[2,3-*b*]indol-3-yl)methanol (13). *anti*-**4b** (0.2 mmol, 78.5 mg) was dissolved in EtOH (3 mL), Raney nickel (4 drops of the commercially available suspension in water) was added, and the reaction mixture was stirred at room temperature under an H_2 balloon overnight. Then the mixture was filtered and washed with ethyl acetate and DCM. The solvent was removed under reduced pressure, and the diastereomeric mixture of **11a** and **11b** (dr = 54/46) was obtained pure. The crude mixture was dissolved in acetone (1.5 mL), and K_2CO_3 (0.4 mmol) was added. The reaction mixture was stirred at 50 °C for 24 h, and the conversion was monitored by ^{1}H NMR. After completion, the solvent was removed, the residue was dissolved in water (5 mL), and this solution was extracted with DCM (3 × 6 mL). The organic phases were collected and dried over Na_2SO_4. The solvent was evaporated under reduced pressure, and the crude product **11a** was dissolved in THF (5 mL). $LiAlH_4$ (2 mmol) was added, and the mixture was heated at 75 °C for 2 h. It was cooled to room temperature and quenched with ethyl acetate (6 mL) and then H_2O (1.2 mL). The resulting mixture was filtered through Celite and washed with ethyl acetate and MeOH. The filtrates were concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (DCM/MeOH 20/1), providing compound **13**: 72% yield over three steps, 31 mg, amorphous solid; ^{1}H NMR (400 MHz, CD_3OD) δ 7.14 (t, J = 8.0 Hz, 1H), 7.01 (d, J = 7.2 Hz, 1H), 6.70−6.66 (m, 2H), 3.72 (d, J = 8.0 Hz, 1H), 3.64 (dd, J = 12.0 and 4.0 Hz, 1H) 3.60 (dd, J = 12.0 and 4.0 Hz, 1H), 3.59−3.53 (m, 1H), 2.80 (s, 3H), 2.10−2.04 (m, 1H), 1.26 (d, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, CD_3OD) δ 21.8, 30.8, 47.2, 52.6, 54.6, 62.4, 111.7, 118.1, 125.3, 128.8, 129.2, 149.3, 179.7; HPLC-MS (ESI) t_r = 2.2 min; $[M + H]^+$ = 217.1 m/z, $[M + H_2O + H]^+$ = 235.3 m/z, $[M + Na]^+$ = 239.1 m/z; $[\alpha]_D^{25}$ = −14° (c = 0.45, MeOH). Anal. Calcd for $C_{13}H_{16}N_2O$ (216.13): C, 72.19; H, 7.46; N, 12.95. Found: C, 72.16; H, 7.43; N, 12.99.

Synthesis of *tert*-Butyl 3-((2*R*,3*R*)-1-Ethoxy-3-nitro-1-oxobutan-2-yl)-2-oxoindoline-1-carboxylate (*syn*-4b). *anti*-**4b** (0.1 mmol, 39 mg) was dissolved in DCM (0.4 mL), and DBU (1,5-diazabiciclo[5.4.0]undec-5-ene, 30 mol %) was added. The reaction mixture was stirred at room temperature for 24 h, and the conversion was monitored by ^{1}H NMR. The solvent was evaporated under reduced

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pressure, and the crude reaction mixture was directly purified by flash chromatography on silica gel (cyclohexane/ethyl acetate 9/1): 70% yield, 27.5 mg, gum; mixture of two diastereoisomers (dr = 70/30); ^{1}H NMR (400 MHz, CDCl3) δ 7.89−7.82 (m, 2H), 7.38−7.27 (m, 3H), 7.21−7.12 (m, 3H), 5.33−5.23 (m, 2H), 4.13 (dd, J = 2.4 and 10.0 Hz, 1H), 4.05 (q, J = 6.8 Hz, 2H), 3.96−3.85 (m, 4H), 3.81 (s, 1H), 1.75 (d, J = 7.2 Hz, 3H), 1.67−1.64 (m, 21H), 1.08 (t, J = 7.2 Hz, 3H), 0.91 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.4, 13.6, 17.9, 18.4, 28.1, 44.4, 44.6, 49.1, 49.4, 61.8, 62.0, 80.9, 81.6, 84.8, 84.9, 115.3, 115.4, 123.5, 123.6, 123.7, 124.6, 124.6, 129.2, 129.4, 140.2, 140.5, 148.9, 168.6, 169.6, 173.0, 173.2; HPLC-MS (ESI) t_r = 10.3 min, 10.4 min; $[M - Boc + H]^+$ = 293.3 m/z, $[M + H_2O]^+$ = 410.3 m/z, $[M + Na]^+$ = 415.3 m/z. Anal. Calcd for $C_{19}H_{24}N_2O_7$ (392.16): C, 58.16; H, 6.16; N, 7.14. Found: C, 58.06; H, 6.18; N, 7.15. To check the optical purity of compound *syn*-**4b**, it was deprotected as previously described and injected in CSP-HPLC.

3-((2R,3R)-1-Ethoxy-3-nitro-1-oxobutan-2-yl)-2-oxoindoline: amorphous solid, mixture of two diastereoisomers (dr = 76/24), the signals of the major isomer have been described; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (bs, 1H), 7.30−7.25 (m, 2H), 7.08 (t, J = 7.2 Hz, 1H), 6.90 (d, J = 8.0 Hz, 1H), 5.25−5.17 (m, 1H), 4.11 (q, J = 6.8 Hz, 2H), 3.91 (dd, J = 2.8 and 10.0 Hz, 1H), 3.87 (d, J = 2.8 Hz, 1H), 1.59 (d, J = 6.4 Hz, 3H), 1.13, (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 17.8, 44.3, 48.4, 61.9, 81.5, 110.0, 122.9, 124.7, 124.9, 129.1, 140.9, 170.3, 176.0; HPLC-MS (ESI) t_r = 7.0 min; $[M + H]^+$ = 293.3 m/z, $[M + Na]^+$ = 315.2 m/z, $[2M + Na]^+$ = 607.4 m/z. Anal. Calcd for $C_{14}H_{16}N_2O_5$ (292.11): C, 57.53; H, 5.52; N, 9.58. Found: C, 57.35; H, 5.51; N, 9.62. CSP-HPLC: IC 90/10 *n*-Hex/IPA for 10 min, then up to 80/20 in 5 min, 80/20 for 20 min, then up to 75/25 in 15 min, 75/25 up to 47 min; flow rate 0.5 mL/min at room temperature; λ 214 nm; t_r(major isomer) = 25.4 min (minor), 34.0 min (major); t_r(minor isomer) = 28.6 min (major), 42.7 min (minor).

Synthesis of ((2*R*,3*R*,3a*S*)-2,8-Dimethyl-2,3,3a,8-tetrahydropyrrolo[2,3-*b*]indol-3-yl)methanol (14). *syn*-**4b** (0.1 mmol, 39 mg) was dissolved in EtOH (2 mL), Raney nickel (3 drops of the commercially available suspension in water) was added, and the reaction mixture was stirred at room temperature under an H_2 balloon overnight. Then it was filtered and washed with ethyl acetate and DCM. The solvent was removed under reduced pressure, and the β-amino oxindole **15** was obtained pure as an oil. The crude **15** was dissolved in THF (3 mL), $LiAlH_4$ (1 mmol) was added, and the mixture was heated at 75 °C for 2 h. The mixture was cooled to room temperature and quenched with ethyl acetate (4 mL) and then H_2O (0.8 mL). The resulting mixture was filtered through Celite and washed with ethyl acetate and MeOH. The filtrates were concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel (DCM/MeOH 20/1), providing compound **14**: 76% yield over two steps, 16.5 mg, amorphous solid.

*(S)-tert-Butyl 3-((2R,3R)-3-amino-1-ethoxy-1-oxobutan-2-yl)-2-oxoindoline-1-carboxylate (**15**):* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (bs, 1H), 7.32−7.23 (m, 2H), 7.15−7.08 (m, 2H), 5.88 (bs, 1H), 4.32 (d, J = 10.0 Hz, 1H), 4.28−4.13 (m, 3H), 3.64 (dd, J = 8.8 and 9.2 Hz, 1H), 1.54 (s, 9H), 1.30−1.26 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 18.0, 28.4, 43.5, 49.0, 51.7, 61.6, 80.0, 124.6, 127.6, 128.0, 128.1, 128.5, 137.4, 153.7, 171.2, 176.2; HPLC-MS (ESI) t_r = 7.7 min; $[M - Boc + H]^+$ = 263.3 m/z, $[M + H]^+$ = 363.4 m/z; $[\alpha]_D^{25}$ = 19° (c = 1.69, CH_2Cl_2). Anal. Calcd for $C_{19}H_{26}N_2O_5$ (362.18): C, 62.97; H, 7.23; N, 7.73. Found: C, 62.77; H, 7.21; N, 7.72.

*((2R,3R,3aS)-2,8-Dimethyl-2,3,3a,8-tetrahydropyrrolo[2,3-b]-indol-3-yl)methanol (**14**):* ^{1}H NMR (400 MHz, CD_3OD) δ 7.14 (t, J = 7.6 Hz, 1H), 6.97 (d, J = 7.2 Hz, 1H), 6.72−6.65 (m, 2H), 3.95−3.88 (m, 1H), 3.75 (dd, J = 7.6 and 10.8 Hz, 1H) 3.66 (d, J = 6.4 Hz, 1H), 3.56 (dd, J = 7.6 and 10.4 Hz, 1H), 2.81 (s, 3H), 2.54−2.47 (m, 1H), 1.22 (d, J = 6.8 Hz, 3H); ^{13}C NMR (50 MHz, CD_3OD) δ 16.0, 30.8, 47.0, 51.3, 60.8, 111.6, 117.9, 124.0, 128.0, 129.2, 149.3, 180.1; HPLC-MS (ESI) t_r = 2.1 min; $[M + H_2O + H]^+$ = 235.3 m/z, $[2M + Na]^+$ = 455.5 m/z; $[\alpha]_D^{25}$ = 15° (c = 0.15, MeOH). Anal. Calcd for $C_{13}H_{16}N_2O$ (216.13): C, 72.19; H, 7.46; N, 12.95. Found: C, 72.16; H, 7.45; N, 13.00.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Text, tables, and figures giving details of the determination of the relative and absolute configurations, ^{1}H and ^{13}C NMR spectra of new compounds, and CSP-HPLC traces. This material is available free of charge via the Internet at http://pubs.acs.org.

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The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes

The authors declare no competing financial interest.

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